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MALARIAL HEMOGLOBINURIA

OUR first case is one of malarial hemoglobinuria. The patient has been in the hospital nearly three weeks, and is now well enough to be discharged.

It is important in discharging any patient to give proper advice with regard to subsequent treatment, if any is indicated, to habits of living or precautions that should be taken to prevent recurrence, and to return visits if desirable. It is especially important to give proper advice in discharging patients who have had malarial hemoglobinuria on account of the danger of relapse and the high mortality of the disease.

This patient is a large negro man, thirty-eight years of age. He has lived in Bolivar County, Mississippi, all his life until about three weeks ago, when he came to New Orleans, where he has worked as a banana loader on the river front. The part of Mississippi, in the delta, from which he comes has had the reputation of being one of the most malarious sections of this country, and up to twenty or thirty years ago there was a great deal of malarial hemoglobinuria there. This form of malaria is now rarely seen there or anywhere else in the United States.

There is much less malaria in that section than there was years ago, but it is still quite prevalent. Hemoglobinuria is practically gone, but malaria still remains. This is quite in accordance with observations made with regard to the decline

of hemoglobinuria and of malaria in other parts of the world where such decline has occurred. Hemoglobinuria declines as malaria declines, and finally disappears long before malaria entirely disappears. It seems that not only malaria but also malaria in considerable concentration is necessary to produce malarial hemoglobinuria.

It is noteworthy that hemoglobinuria rarely occurs except in cases of malaria of long duration. It is more likely to occur in cases that have relapsed or have been reinfected from time to time over a period of months or years. It practically never occurs with the first attack of malaria.

The history given by this man is to the effect that he has had spells of chills and fever several different times during his lifetime, and that he was "down during the whole fall and nearly died" five years ago from "swamp fever and hematuria," as it was diagnosed to be by his physician. He had two different attacks of "hematuria" associated with attacks of chills and fever, and, in addition, he had fever for a while which was not accompanied by chills or hematuria. However, it was thought to be due to the same cause—malaria.

After a long, slow convalescence he regained his health and remained well until the fall two years ago, when he had another attack of chills and fever. Within an hour or two following the second chill, which was very severe, he developed "hematuria." He had started taking quinin on that same day and he felt sure that the quinin caused the "hematuria," as he had been told previously that quinin was sure to cause it. A physician was called and he gave more quinin by injection into the buttocks. The hematuria continued for two or three days, but there were no further chills. The patient slowly recovered while taking some kind of "poison medicine" (probably arsenic) which the doctor said would take the place of quinin.

Since that attack two years ago he has remained well until just before his admission to the hospital here three weeks ago. He had a severe chill one morning, followed by fever, for which he took two large capsules of quinin given him by the company physician. Within six hours his urine was "bloody" and he

rapidly got very sick, whereupon he was sent to the hospital the next morning.

Upon admission the man was greatly depressed, temperature 101$\frac{1}{5}$° F., pulse 112, and weak. He appeared quite restless and severely ill. He passed a little urine which was a very dark sherry wine color, but this cleared considerably within a few hours. Another chill occurred, accompanied by further depression and return of the very dark urine.

Physical examination failed to disclose anything except a palpable spleen and doubtful, slight enlargement of the liver.

Examination of the blood made within an hour after admission showed 9400 leukocytes, hemoglobin 70 per cent., total erythrocytes 4,120,000, and a few crescents, but no other malaria parasites. Following the second chill a very few ring form parasites were found, but after that time no parasites have been found, although the blood has been examined frequently. This is not an unusual experience. Malaria parasites are present in all cases of malarial hemoglobinuria, and they may be found during the first few hours thereafter in most cases. They are not found in even half of the severe cases after the first twenty-four hours. The longer the time that has elapsed since the onset of the hemoglobinuria, the less likely are we to find parasites.

A student asks how we explain the reduction or disappearance of malaria parasites, which are supposed to be the cause of the disease, at the same time that the most noteworthy symptoms continue or increase.

Perhaps the best we can do is to offer a theoretical answer to your question. The exact manner in which hemoglobinuria in malaria is produced is not definitely understood. We do know, however, that a condition exists in which hemolysis of more or less of the blood-cells occurs. There is every reason to suppose that less resistant or injured cells would be affected most by this hemolysis. Malaria parasites live on or in red blood-cells and gradually consume or destroy the host cells. Cells injured by the presence of malaria parasites are naturally less resistant than the unparasitized cells, and therefore would be affected more by the hemolytic agent present in these particular

cases of malaria than the normal cells would be. If the cells containing parasites are hemolyzed, the parasites soon die or are phagocytized and destroyed. We have often observed that malaria parasites will grow in the test-tube only in normal healthy cells, and that they will not grow in cells that have been injured, even though the injury may be very slight, such as would result from such things as addition of fluids that are not exactly isotonic, which have the slightest hemolytic effect. Anything tried so far that causes the slightest hemolysis kills malaria parasites or, at least, prevents them from growing in otherwise favorable test-tube cultures. The same thing seems to occur with parasites in the circulating blood of patients who develop that peculiar condition which causes hemoglobinuria. The parasites die out rapidly in most cases and, therefore, are found in smaller numbers or not at all after the first few hours or the first day or two of the attack. The hemolysis tends to cure the malaria, and this is the explanation for the fact that so many cases recover without quinin treatment. The hemolysis kills parasites.

Another student asks whether I think quinin really does cause hemoglobinuria.

I do think that it does in otherwise susceptible individuals. Certain individuals seem to have a natural or acquired unusual tendency to develop hemoglobinuria in malaria. They may develop it without having taken any quinin, but it is certainly more likely to occur following large doses of quinin. I myself have seen a fatal case of malarial hemoglobinuria in which no quinin had been taken and none was given during the course of the disease.

Our present patient is a good illustration of the special susceptibility to hemoglobinuria that certain individuals possess. His history indicates that he has had hemoglobinuria in the course of three separate attacks of malaria, each one of which was, in all probability, the result of separate and distinct infections. It was three years between the first and second attacks and two years between the second and the third, still he has had hemoglobinuria with each malarial attack. A given malarial

infection very seldom lies dormant over a period of two years and practically never over three years. This patient has had hemoglobinuria with every attack of malaria plus quinin, whereas other patients with the same kind of infection taking even very much more quinin do not have it. The patient has an unusual susceptibility or tendency to hemoglobinuria. In such an individual quinin tends to precipitate this condition or to increase it, although it would not cause hemoglobinuria in the same individual if he did not have active malaria at the time. In fact, this patient is now taking 10 grains of quinin daily and has been taking this much or more ever since his third day in the hospital.

This brings up the question of the use of quinin in treatment of malarial hemoglobinuria. There are many physicians who feel that it is harmful and should be avoided in all cases. They say if you give quinin the patients will die. Others are equally as positive in their opinion that if you do not give quinin the patients will die. It leaves one confused and in doubt as to what should be done. We are faced with a dilemma that is most confusing. We know that the primary essential cause of the condition is malaria and that quinin is our only specific remedy for malaria. On the other hand, we know that quinin actually may precipitate hemoglobinuria in an otherwise susceptible individual who has malaria, and that it tends to increase hemoglobinuria when the condition already exists. What shall we do?

In the first place, let us keep clearly in mind the fact that the only purpose of giving quinin in malaria is to destroy the parasites, and that it only kills those in the circulating blood, but does not kill those lodged in the capillaries in the different organs and tissues of the body except as they become dislodged and appear in the blood-stream. We should also remember that the hemolysis which causes the hemoglobinuria also tends, at least, to reduce or kill the parasites in the circulating blood. The effect of a very small amount of quinin, added to that of the hemolysis, is usually all that is necessary to rid the blood of parasites entirely. The smaller the amount of quinin used, the

less harm it will do, so far as the hemolysis is concerned and the circumstances make it unnecessary at present to give large doses. Therefore one would certainly avoid the usual large doses and give the very minimum amount that promises to give the desired result of killing the parasites present in the circulating blood. In fact, if there are no parasites found in the blood it is questionable whether any quinin should be given until after the hemoglobinuria has ceased. The objection to this procedure is that the hemoglobinuria often does not cease, but, on the contrary, chills occur, each one followed by an increase in the hemoglobinuria and the rapid anemia and other distressing symptoms, and not infrequently death occurs. On the other hand, if the patient can be gotten on quinin, even in small doses, the probability of further chills with the accompanying increase of other symptoms is very much less.

When patients are confined to bed on very light diet and the bowels are kept well open, very small doses of quinin accomplish as much in controlling symptoms and parasites as much larger doses under the opposite conditions. Even 5 grains or less will often control the symptoms and parasites under these circumstances. This fact and the further fact that we know that quinin tends to increase the hemoglobinuria indicate that very large doses should not be given.

This patient was given 5 grains of quinin bimuriate with urea intravenously daily for three days, after which he was put on 5 grains of quinin sulphate by mouth for three days and then on 5 grains night and morning until the present time. We are now about to discharge him from the hospital, and our chief purpose in presenting him is to emphasize what we believe to be the proper advice to be given to such patients when they are discharged.

The standard treatment for malaria is "10 grains of quinin sulphate by mouth three times daily for a period of three or four days to relieve the clinical symptoms, followed by 10 grains every night before retiring for a period of eight weeks to cure the infection." This cures the infection in more than 90 per cent. of cases. A few remain infected and may relapse even after

eight weeks of such treatment. It is most important that those who have had hemoglobinuria should be cured of their infection, and not take any chances on a relapse with the danger of another attack of hemoglobinuria. In such cases it is best to make assurance doubly sure and to continue the treatment somewhat longer than in the ordinary case. It should be continued three or four weeks longer than the usual eight weeks in ordinary cases. Although quinin tends to increase hemoglobinuria or to precipitate it in cases of active malaria in susceptible individuals, it does not do this after the active malaria has stopped. It is important, therefore, that after the patient is once on quinin it should be continued without interruption until the infection is cured.

Unless we give the patient impressive advice and instructions, the proper treatment may not be carried out. We have very carefully explained to this man that it is necessary for him to continue to take the quinin for nine weeks from the present time to be sure to get rid of the malaria and avoid the danger of another attack of hemoglobinuria, which he realizes is very dangerous. Notwithstanding the fact that he is an uneducated negro laborer, he has sufficient intelligence to fully understand the advice we have given him, and it is not difficult to secure his unbounded confidence in our advice. It will be well for him to come back to see us in a few days, and we will instruct him to do so. However, so far as the malaria is concerned, we know now just as much about the treatment to be followed as we will ever know. We know now that he should continue the quinin for the full period. We ask him if he understands our instructions and if he will carry out the treatment. He answers, "Boss, I shore will," and he will do it.

HEALTH EXAMINATION

Our next case is that of a man who came to us for a thorough examination. He states that, so far as he knows, he is perfectly well, but that he came upon the advice of his brother, who lives in Hagerstown, Maryland, and who has been writing to him about the activities of the health organization there in promoting the health of the people in the community, and especially the matter of periodic health examination. His brother wrote him that they were advising everybody to visit a physician and have a health examination made about once every year. Many adopt the rule of having the examination on or about their birthday each year. His brother had been impressed so much because, in the course of his examination, it was discovered that he had a mild form of diabetes, although he had previously considered himself to be in good health. This has made a convert of the brother to the importance of the periodic health examination, and he has passed on the advice to our present patient and, no doubt, to others. This is a good example of the far-reaching effect of education along health lines. A man living in New Orleans is influenced beneficially by health work done in Hagerstown, Maryland.

A movement advocating and promoting health examinations has been growing throughout the country for several years, although very slowly, it is true. This very important health service has been promoted chiefly by public health agencies, insurance companies, so-called "life extension institutes," etc. The national, state, and local organizations of the medical profession have also taken some steps in this direction in many instances, but the results thus far, from all of these activities, have been negligible in comparison with the needs and possibilities. I believe that much of the failure or slow progress in popularizing periodic health examinations has resulted from the fact that the practising physicians generally have not recog-

nized the opportunity for useful service and remunerative work that lies before them in this field, and from the fact that there has been a tendency on the part of the agencies promoting this work to act independently of the practising physicians and not to encourage their co-operation and assistance. Practising physicians have failed to realize that they are well prepared, or at least should be, to make these examinations, and that many people want and will pay for such service when they know that they can get it. A capable, conscientious physician locating in almost any town in this country, who would offer this kind of service along with his other services in the treatment of disease, would soon have a good paying practice and become one of the most useful physicians of the community. There is hardly anything that would help one to quickly get a start and a good practice in a community, more than this would. Looking at it either from a selfish standpoint or from the standpoint of duty, greater activity in this direction on the part of practising physicians is indicated, and this applies especially to the young man in a new location.

This patient—or shall we call him a health client—has been thoroughly examined by Dr. P., and we are now ready to give him our findings and to give him such advice or treatment as is indicated by conditions found. Dr. P.'s examination has been quite similar to that of any other patient who came with a definite complaint of ill health. The examination consists of a carefully taken history, thorough physical examination, and a reasonable amount of ordinary routine clinical laboratory examination. The purpose is served in most cases without recourse to extraordinary examination procedures of any kind.

This man is thirty-six years of age and is a salesman in a shoe store. The personal and family history fails to reveal anything significant or indicative of any particular disease tendency. The physical examination has been entirely negative. Not a single abnormal or disease condition has been found except poor teeth. He has bridges replacing absent teeth in both upper and lower jaws and, in addition, he has three or four filled cavities and at least two other unfilled cavities. His

teeth are dirty and most of them have collections of tartar at the gum margins. The condition of his mouth and teeth is unhygienic and he is rapidly losing his teeth, although he is still a comparatively young man. He states that two of the teeth he lost had only small cavities, but that they got loose and were removed on this account. We find that there has been considerable recession of the gums around several of his teeth, and that at least two or three of them are loose enough to move considerably upon manipulation. But what is much more significant is the deep pus pockets around and between some of the teeth. A suitable instrument, a dental scaler, may be passed almost to the apex of the root of this tooth. Here is another and still another deep pocket. Pressure on the gums over these pockets brings to the surface a small amount of pus. We remove some of the pus from one of these pockets with the tip of a scaler and spread it on a slide for microscopic examination. Please note the simple technic by which I have removed this material or specimen and also note how easy it is to prepare the specimen and examine it under the microscope. An effort should be made to scrape or remove the material from the depth of the lesion and not merely from the edge or surface. A suitable dental scaler is the only instrument that I have ever found that is suitable for the purpose.

After being allowed to dry, the slide is fixed with heat by passing it through the flame once or twice in the usual way for fixing pus or other similar material. It is then stained with carbolfuchsin for less than half a minute, followed by Löffler's methylene-blue solution half to one minute. Wash after this, but it is not necessary to wash between the two stains. Dry and examine with the oil immersion lens. If you have never seen such specimens this will be a revelation to you. Regardless of how faithfully one intends to avoid encroaching upon the field of the dentist, every student of medicine owes it to himself to make at least a few of such examinations, so as to be able to appreciate the nature and the importance of this disease, pyorrhea, from which, combined with caries, most people sooner or later lose their teeth.

Let us see what we find under the microscope in this specimen which we have just prepared. There are a great many pus-cells and a few blood-cells. Next we note a good many amebæ. These are mostly stained somewhat darker blue than the other cells, and practically all of them contain one to several very dark stained bodies which are the remains of the nuclei of pus-cells that have been phagocyted by these amebæ. We can see some remaining cytoplasm of the cell around some of these nuclei, but in most instances the cytoplasm has already been digested away. The amebæ seem to feed on these pus-cells.

In addition, we also find large numbers of bacteria of different kinds. There are cocci, bacilli, and spirochetes in most specimens of this kind. In this particular specimen I find staphylococci in large numbers and also quite a few spirochetes. These amebæ move about in the pyorrhea pocket or lesion and burrow to a considerable extent into the granulation tissue of the lesion. Incidentally they carry mechanically the much smaller bacteria and thereby help at least to keep up the suppurative process.

Our first thought is to send this man to the dentist for proper treatment, but it will be profitable for us to discuss the treatment a little further. He has had considerable dental service, as is evidenced by the amount of repair, removals, and replacements he has. Notwithstanding all of this dental service he has received and the many visits he has paid to the dentist, he still is slowly but surely losing his teeth from an unnecessary and preventable disease. For some reason or other he has not received impressive or effective advice about oral hygiene and how to control and prevent this unnecessary loss of his teeth. It is possible that all the attention was given to the mechanical treatments for which the dentist was consulted, as is so often the case, and that prevention of further progress or spread of the same disease to other teeth was entirely overlooked. It is also possible that the patient did not heed such good advice as may have been given him. At any rate, this patient's greatest need is to get such relief as he can for the damage that has already been done, but especially to learn how to prevent further damage. This is

very simple, and although the dentist should be looked to for it, the physician cannot afford to disregard the matter or to assume an attitude of blissful ignorance.

A man's health, comfort, and satisfaction of life are greatly influenced by his teeth. The man who loses his teeth while still young, as this man is doing, cannot masticate, enjoy, and digest his food as well as another who has good teeth until old age. He probably will not live as long. At any rate, his health will be more or less impaired by the long period of suppuration and incident absorption of toxic material.

What this patient needs is to go to his dentist for thorough cleaning of his teeth and for such repairs and treatment as are indicated. He should visit the dentist every few months during the remainder of his life for cleaning and examination, to discover any cavities or other defects that may develop in the future. But what he needs most of all is to learn to brush and clean his own teeth properly. A clean tooth never decays and suppuration of gums does not occur in a clean mouth. All that is necessary to prevent all of the diseases of the teeth and gums which this man has had is to keep the teeth and mouth clean. In fact, further progress of the disease can be controlled almost as easily, although it is a fact that after so much damage has occurred greater vigilance is necessary.

Our patient admits that he brushes his teeth only very irregularly and that almost entirely in the morning after arising. Most people who brush their teeth do so in the morning upon arising, when, as a matter of fact, it is many times more important to brush them at night before retiring. It is bacterial decomposition of food remnants, particles or solution, which produce the damage to the teeth and gums. If all food is removed from the mouth no such decomposition can occur. If one neglects to remove all traces of food from the mouth at night, decomposition goes on through the night, and the mouth is very foul the next morning. The need for brushing the teeth upon arising is felt. If, on the other hand, all traces of food are removed by proper brushing and by very thorough rinsing of the mouth, there is less need for brushing the teeth upon arising in the morning.

The majority of people who brush their teeth and attempt to take good care of them fail in their purpose in two particulars especially. One is the neglect to cleanse the teeth and mouth at night before retiring, and the other is failure to thoroughly rinse the mouth and teeth after brushing so as to remove every trace of food from between the teeth. The most thorough brushing falls very far short of its purpose unless it is followed by very thorough rinsing. If, after you have brushed your teeth in the usual way and have casually rinsed the mouth as it is usually done, you then very thoroughly rinse by forcing water back and forth between the teeth, you will be surprised to see the amount of food particles and food in solution that are removed by this special effort. When this is allowed to remain it rapidly decomposes and produces substances, mostly acids, which cause decay and other damage to the teeth and gums.

It so happens that our examination of this man has revealed nothing abnormal whatever except a bad condition of his teeth. He should return about one year from now for another health examination, and he, like other people, should continue to have such examinations at proper intervals throughout the balance of his life. The main purpose is to discover defects or diseases in their early stages when there is more chance that they may be remedied. The bad condition of his teeth on which we are giving him good advice has existed for a long time, and he would be much better off if he had received and heeded the advice we are now giving him ten, fifteen, or even twenty years ago. If he had, he would now have a full set of sound teeth.

In conclusion, I would emphasize the fact that any well-qualified practising physician is also qualified to make these health examinations. It is a part of his function in the community, and he is just as much entitled to reasonable pay for such service as he is for any other work he does. If this were a private patient he should be charged, and, no doubt, he would be quite willing to pay for our services today.

CLINIC OF DR. ALDO CASTELLANI

TULANE UNIVERSITY AND CHARITY HOSPITAL

INTERNAL MYCOSES

DISEASES of fungal origin are comparatively frequent in Louisiana and other Southern States. I propose, therefore, in this and subsequent hours to discuss certain conditions of fungal etiology not rarely met with in practice.

A disease due to fungi is called a mycosis. Fungi, or mycetes, may be defined for practical purposes as vegetal organisms which are of higher development than bacteria, from which they differ principally in the following two points:

1. They are of larger dimension.
2. They reproduce by means of spores and not by fission.

It must be kept in mind that "natura non fat saltus," and there are vegetal organisms on the borderline between the two groups which it may be difficult to classify, some authorities placing them among the bacteria, others among the fungi; it is well known also that there are bacteria which multiply by spores in addition to fission. It must also be remembered that until comparatively recently the term "fungi" was used to cover both fungi and bacteria.

Fungi may affect any organ and system of the human body, the integumentary system being the most frequently, the nervous system the most rarely, affected.

Mycoses may be separated into two large groups: (*a*) Internal mycoses; (*b*) external mycoses, or dermatomycoses. I propose to briefly discuss the following mycoses: Thrush, including stomatitis cryptococco-bacillaris, tonsillomycoses, certain mycoses of the organs of special senses, certain mycoses of the bronchi and lungs, certain mycoses of the genito-urinary tract.

THRUSH

In all text-books the statement is found that the disease is caused by *Oïdium albicans*, Robin (synonyms: *Monilia albicans*, *Saccharomyces albicans*, *Endomyces albicans*), but very different descriptions have been given of this organism. Some authorities describe it as non-liquefying gelatin, others as liquefying this medium. Some observers have stated that the organism clots milk, others that it has no action on this medium. These different descriptions merely mean, as I noted some years ago, that there is a plurality of species of the thrush fungus. Since 1906, in a series of researches carried out in tropical countries and in the temperate zone, I have endeavored to demonstrate that thrush may be caused by different fungi, and that, in reality, the term "thrush" does not cover one affection only, but a group of clinically similar conditions due to different fungi.

Fungi Found in Thrush.—The fungi I have so far isolated from cases of thrush in the tropics and in temperate climates may be classified as follows:

(*a*) Fungi Imperfecti:
- Family Oösporaceæ Saccardo:
  - Genus Monilia Persoon.
  - Genus Oïdium Link.
  - Genus Cryptococcus Kützing.
- Order Hemisporales Vuillemin:
  - Genus Hemispora Vuillemin.

(*b*) Ascomycetes:
- Family Saccharomycetaceæ Rees:
  - Genus Saccharomyces Meyen.
  - Genus Willia Hansen.
- Family Endomycetaceæ Rees:
  - Genus Endomyces Rees.

Fungi of Genus Monilia Persoon.—These are the fungi most commonly found in thrush. The botanic description of these fungi may be found in previous publications of mine and also in Castellani and Chalmers' "Manual of Tropical Medicine," p. 1079. It suffices to say here that the genus Monilia as understood today by medical mycologists, Pinoy, etc., does not correspond to the original genus Monilia as defined by Persoon in 1797. "Stipitata aut effusa byssoidea, Fila moniliformis articulata," nor to the definition of Saccardo and other botanists, who state that these fungi are characterized by the sporophores being simple or subsimple and producing by constriction at the extremities a chain or large lemon-shaped conidia, often provided with a disjunction apparatus. The tendency has been in recent years to extend the term "Monilia" to all yeast-like fungi, possessing a certain amount of mycelium and never showing ascus formations. In the lesions the vegetal

body (thallus) is composed of mycelial threads of rather large size, often showing arthrospores, and numerous free oval or roundish budding elements are seen, while mycelial filaments are very scarce or absent. These fungi, as a rule, ferment, with production of gas, glucose, and often other sugars.

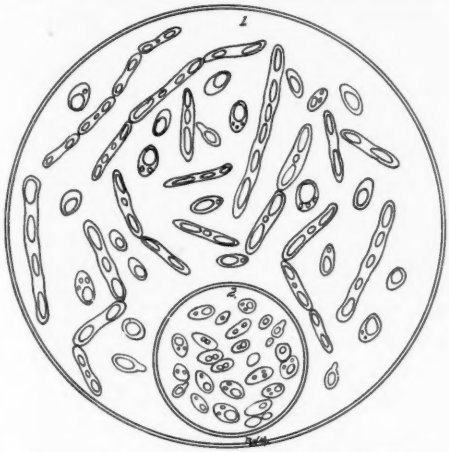

Fig. 177.—1, Monilia in the lesions. 2, Preparation from glucose-agar culture.

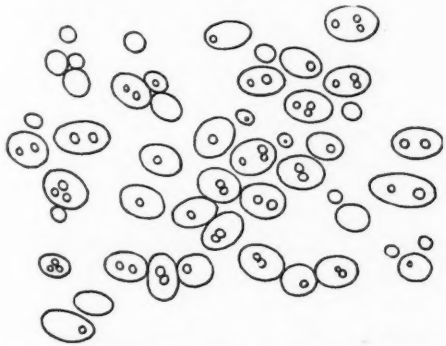

Fig. 178.—Monilia tropicalis from glucose-agar culture.

Classification of Monilias.—Monilias may differ in size and shape principally with regard to their conidia or spores. In fact, according to the shape of the spores, monilias might be divided into two groups: (*a*) With roundish spores; (*b*) with oval or elongated spores. Morphologic characters, however, will not carry us much further, and for several years I have suggested a

biochemical or physiologic classification of monilias based principally on their fermentative reactions in various sugars. According to this classification monilias may be separated into the following groups:

1. *Balcanica Group.*—Gas produced in *glucose* only. Principal species: *Monilia balcanica* Cast. *Monilia parabalcanica* Cast.

2. *Krusei Group.*—Gas produced in *glucose* and *levulose.* Principal species: *Monilia krusei* Cast., *Monilia parakrusei* Cast., *Monilia castellanii* Re.

3. *Pinoyi Group.*—Gas produced in *glucose, levulose, maltose.* Principal species: *Monilia pinoyi* Cast., *Monilia nabarroi* Cast.

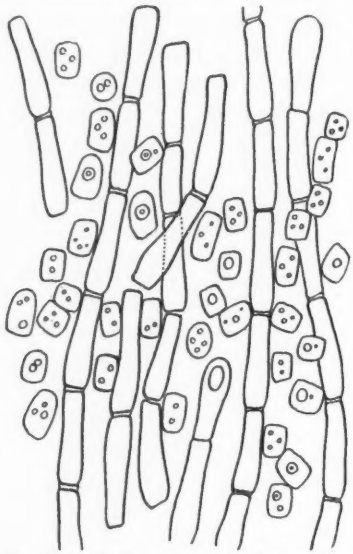

Fig. 179.—Oïdium asteroides from culture.

4. *Metalondinensis Group.*—Gas produced in *glucose, levulose, maltose,* and *galactose.* Principal species: *Monilia metalondinensis* Cast., *Monilia pseudometalondinensis* Cast.

5. *Tropicalis Group.*—Gas produced in *glucose, levulose, maltose, galactose,* and *saccharose.* Principal species: *Monilia tropicalis* Cast., *Monilia metatropicalis* Cast.

6. *Rhoi Group.* Gas produced in *dextrose, levulose, galactose,* and *saccharose.* Principal species: *Manilia* rhoi Cast.

7. *Bronchialis Group.* Gas produced in *dextrose, levulose, maltose,* and *saccharose.* Principal species: *Monilia bronchialis* Cast.

8. *Guillermondi Group.*—Gas produced in *glucose, levulose, saccharose,* and *raffinose.* Principal species: *Monilia guillermondi* Cast., *Monilia pseudoguillermondi* Cast.

9. *Macedoniensis Group.*—Gas produced in *glucose, levulose, galactose, saccharose,* and *inulin.* Principal species: *Monilia macedoniensis* Cast., *Monilia macedoniensoides* Cast., *Monilia chalmersi* Cast.

10. *Pseudotropicalis Group.*—Gas produced in *lactose* and other carbohydrates. Principal species: *Monilia pseudotropicalis* Cast.

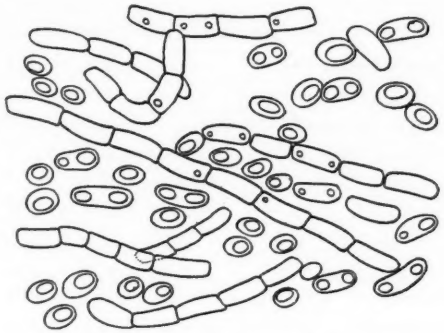

Fig. 180.—Oïdium rotundatum from culture.

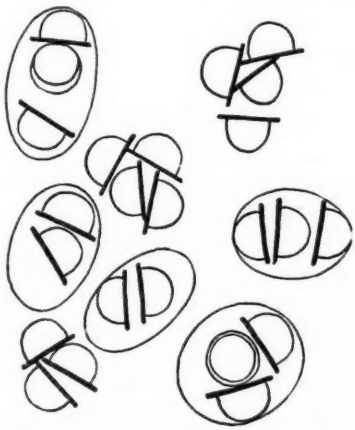

Fig. 181.—Willia anomala, Hansen, ascospores.

11. *Pseudolondinensis Group.*—Gas produced in *dextrin* in addition to other carbohydrates. Principal species: *Monilia pseudolondinensis* Cast., *Monilia pseudolondinoides,* Cast., *Monilia africana* Macfie.

12. *Zeylanica Group.*—No gas produced in any sugar. Principal species: *Monilia zeylanica* Cast., *Monilia zeylanoides* Cast., *Monilia macroglossiæ* Cast.

BIOCHEMICAL CHARACTERS OF

	Glucose	Levulose	Maltose	Galactose	Saccharose	Lactose	Mannitol	Dulcitol	Dextrin	Raffinose	Arabinose	Adonitol	Inulin	Sorbitol	Starch
Monilia zeylanica Castellani----------	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Monilia zeylanoides Castellani----------	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Monilia (cryptococcus) macroglossiae Cast.-	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Monilia balcanica Castellani----------	G	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Monilia parabalcanica Castellani----------	G	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Monilia krusei Castellani----------	G	G	0	0	0	0	0	0	0	0	0	0	0	0	0
Monilia parakrusei Castellani----------	G	G	0	0	0	0	0	0	0	0	0	0	0	0	0
Monilia (cryptococcus) castellanii Re------	G	G	0	0	0	0	0	0	0	0	0	0	0	0	0
Monilia pinoyi Castellani----------	G	G	G	0	0	0	0	0	0	0	0	0	0	0	0
Monilia nabarroi Castellani----------	G	G	G	0	0	0	0	0	0	0	0	0	0	0	0
Monilia metalondinensis Castellani---------	G	G	G	G	0	0	0	0	0	0	0	0	0	0	0
Monilia pseudolondinensis Castellani-------	G	G	G	G	0	0	0	0	G	0	0	0	0	0	0
Monilia alba Castellani----------	G	G	G	G	0	0	0	0	0	0	0	0	0	0	0
Monilia pseudolondinoides Castellani-------	G	G	G	G	0	0	0	0	G	0	0	0	0	0	0
Monilia africana Macfie, 1921----------	G	G	G	0	G	0	0	0	G	G	0	-	0	0	0
Monilia albicans Robin, emend. Castellani and Chalmers----------	G	G	G	G	0	0	0	0	0	0	0	0	0	0	0
Monilia tropicalis Castellani----------	G	G	G	G	G	0	0	0	0	0	0	0	0	0	0
Monilia metatropicalis Castellani----------	G	G	G	G	G	0	0	0	0	0	0	0	0	0	0
Monilia rhoi Castellani----------	G	G	0	G	G	0	0	0	0	0	0	0	0	0	0
Monilia guillermondi Castellani----------	G	G	0	0	G	0	0	0	0	G	0	0	0	0	0
Monilia pseudoguillermondi Castellani------	G	G	0	0	G	0	0	0	0	0	0	0	0	0	0
Monilia macedoniensis Castellani----------	G	G	0	G	G	0	0	0	0	0	0	0	G	0	0
Monilia macedoniensoides Castellani--------	G	G	0	G	G	0	0	0	0	0	0	0	G	0	0
Monilia chalmersi Castellani----------	G	G	0	G	G	0	0	0	0	0	0	0	G	0	0
Monilia parachalmersi Castellani----------	G	G	0	G	G	0	0	0	0	0	0	0	G	0	0
Monilia bronchialis Castellani----------	G	G	G	0	G	0	0	0	0	0	0	0	0	0	0
Monilia pseudotropicalis I ----------	G	G	0	G	G	G	0	0	0	0	G	0	0	0	0
Monilia pseudotropicalis II ----------	G	G	0	G	G	G	0	0	0	0	0	0	G	0	0
Monilia pseudotropicalis III----------	G	G	0	G	G	G	0	0	0	0	0	0	G	0	0
Monilia pseudotropicalis IV ----------	G	G	0	G	G	G	0	0	0	G	0	0	G	0	0

Note: G = production of gas; C = production of clot;

CERTAIN MONILIAS

Glycerine	Inositol	Salicin	Amygdalin	Isodulcitol	Erythrite	Gelatine	Serum	Litmus Milk		REMARKS
0	0	0	0	0	0	0	0	C	Yellowish	
0	0	0	0	0	0	0	0	0	White	Produces no discoloration of lead agar.
0	0	0	0	0	0	0	0	0	White	Produces black discoloration of lead agar
0	0	0	0	0	0	0	0	0	White	
0	0	0	0	0	0	0	0	C	White	
0	0	0	0	0	0	0	0	0	White	
0	0	0	0	0	0	0	0	C	White	
0	0	0	0	0	0	0	0	0	Yellowish or reddish-brownish	
0	0	0	0	0	0	0	0	0	White	
0	0	0	0	0	0	0	0	C	White	
0	0	0	0	0	0	0	0	0	White	
0	0	0	0	0	0	0	0	0	White	
0	0	0	0	0	0	0	0	C	White	
0	0	0	0	0	0	0	0	C	White	
0	0	0	0	0	0	0	0	0	White	
0	0	0	0	0	0	0	+	0	White	
0	0	0	0	0	0	0	0	0	White	
0	0	0	0	0	0	0	0	C	White	
0	0	0	0	0	0	0	0	0	White	
0	0	0	0	0	0	0	0	0	White	
0	0	0	0	0	0	0	0	C	White	
0	0	0	0	0	0	0	0	0	White	
0	0	0	0	0	0	0	0	C	White	
0	0	0	0	0	0	0	0	0	Dark brown	
0	0	0	0	0	0	0	+	C	White	
0	0	0	0	0	0	0	0	0	White	
0	0	0	0	0	0	0	0	C	White	
0	0	0	0	0	0	0	0	0	White	
0	0	0	0	0	0	0	0	C	White	
0	0	0	0	0	0	0	0	0	White	

0 = negative result; viz., gas absent, no clotting.

It is important to note that some monilias after a few transplantations lose some of their fermentative characters or these may become altered. Hence in certain cases the determination of species is possible only when using recently isolated strains.

Hemispora rugosa Cast.—This fungus was first isolated by me from a case of mycotic tonsillitis in 1910, and observed in a case of thrush by Pijper in 1915. It grows abundantly on glucose agar, producing a brownish growth with a crinkled surface. Two varieties can be distinguished; one liquefying gelatin, the other having no such action on the medium.

Fungi of the Genus Willia Hansen.—These fungi are characterized by the peculiar bowler-hat shape of their ascospores. I isolated a fungus belonging to this genus in Macedonia from a case of thrush in a gypsy. In sugar broths it formed a thick pellicle containing air bubbles. It produced gas in glucose and levulose only. Old cultures on solid media contained asci with two to four spores of the peculiar hat-like appearance. The fungus seemed to be somewhat similar to *Willia anomala* Hansen.

Fungi of the Genus Cryptococcus Kutzing.—These fungi may occasionally cause thrush; they are identical to Saccharomyces, but asci are never found.

Fungi of Genus Endomyces Link.—The fungi are on superficial examination extremely similar to those of the genus Monilia, budding elements and mycelial threads being found in the lesions, and mostly budding elements in cultures. There is, however, a very important character which differentiates these fungi. In old cultures of endomyces asci are present. Only once have I come across a case of thrush due to a true endomyces, in Macedonia in 1917. I considered it to be *E. vuillemini* Landrieu.

Fungi of Genus Saccharomyces Meyen.—In the Balkans I found a case of thrush due to a typical saccharomyces. Abundant asci were present in old cultures. Fungi of this genus are characterized by the vegetative body consisting only of budding elements, and by the presence of asci in cultures. The saccharomyces isolated by me ferments, with production of gas, glucose, levulose, galactose, maltose, and saccharose. It does not clot milk, which, however, may occasionally become acid. Gelatin and serum are not liquefied.

Fungi of Genus Nocardia Toni and Trevisan, 1889.—A variety of thrush has been described in which the patches consist of enormous numbers of bacillus-like fungi of the genus Nocardia, but this kind of thrush is extremely rare. Fungi of the genus Nocardia are characterized by being bacillus-like, very thin (1 micron or less), gram positive, and at times acid-fast.

Etiology of Thrush in New Orleans and Louisiana.—Last year Dr. Turner and I investigated 14 cases of thrush in the wards and clinics of Charity Hospital. The patients had contracted the affection in New Orleans or other places in Louisiana. In 10 cases we found *Monilia pinoyi*, in 1 case *M. tropicalis*, in 1 case *M. metalondinensis*, in 1 case an *oïdium*, probably *Oïdium matalense*, in 1 case we found two organisms associated together: *Monilia tropicalis* and *M. krusei*.

Clinical Varieties of Thrush.—I have always endeavored to study the cases of thrush I have observed both mycologically and clinically, to see whether different groups of fungi are causing different types of thrush. In my experience two principal varieties of thrush may be distinguished: (1) The white type—by far the most common—characterized by the cream-white color of the patches; this is practically the only type of thrush found in temperate zones; (2) the yellow, or yellowish-brown type; characterized by the yellowish, occasionally brownish color of the patches. The first type is usually caused by species of the genus *Monilia*, the commonest being *M. pinoyi*, rarely by *Oïdium matalense* Cast., by *Endomyces vuillemini* Landrieu, and fungi of the genera *Saccharomyces* Meyen and *Willia* Hansen. The second type is usually caused by *Hemispora rugosa* Cast., and occasionally by *Oïdium rotundatum* Cast. The prognosis is somewhat different in the two varieties: in the white variety it is generally good except in old people or cachectic individuals. The prognosis in the yellowish-brown variety is not so favorable, as the condition is very resistent to treatment, and may last for many months.

STOMATITIS CRYPTOCOCCO-BACILLARIS

The appearance of the lesions is quite different from ordinary thrush. The patches, which are generally of large dimensions, are hardly raised at all, and are not cream white; they have the appearance of a thin translucid whitish film covering parts of the oral mucosa, occasionally giving the impression of being patches of incipient diffused leukoplakia, but the microscopic examination of scrapings will clear the diagnosis. The first 2 cases of this stomatitis I observed in Central America; recently I have seen a case of the same, or of a very similar condition, in England, but the investigation of this case has not yet been completed. The condition seems to be due to a very delicate yeast-like fungus which I have called *Cryptococcus graciloides*, living in symbiosis with a bacillus, *Bacillus vermiculoides*.

Yeast-like Fungus (*Cryptococcus graciloides* Castellani, 1925).—Very delicate yeast-like organism. Gram-positive, not acid-fast. Each cell is roundish or more often oval, with frequently a flask-like shape. In prepara-

tions from the cultures the average maximum longitudinal diameter of most cells is 3 to 4.5 microns, and the maximum average transverse diameter is 2 to 3 microns.

Cultural and Biochemical Characters.—Glucose Agar.—Minute colonies somewhat streptococcus-like.

McConkey Lactose Agar.—Minute colonies, but growth often more abundant than on glucose agar.

Gelatin and Serum.—Growth exceedingly scanty; neither of the media is liquefied.

Lead Agar.—No evident darkening of the medium.

Glucose and Other Sugar Peptone Waters.—Apparently no production of acidity or gas, but the organism grows extremely scantily in these media, and sometimes no growth at all takes place.

Classification of the Organism.—As the fungus is morphologically yeast-like it comes under the general heading "Yeast-like Fungi" or "Budding Fungi."

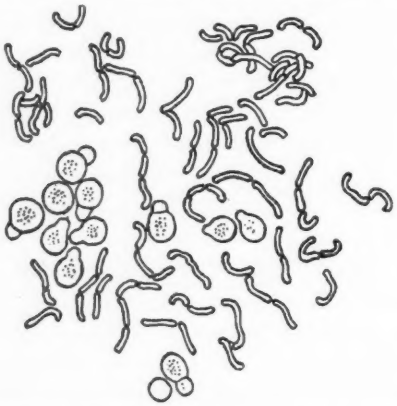

Fig. 182.—Symbiosis of Cryptococcus graciloides and B. vermiculoides from glucose-agar culture.

This yeast-like fungus never shows presence of asci, mycelium is completely absent, the budding takes place by one budding at a time; the organism does not produce a thick pellicle in fluid-sugar media; it should, therefore, be placed in the genus *Cryptococcus*. The peculiar flask-like appearance often shown by this fungus might be an argument to place it in another genus, the genus *Pityrosporum*, which is said to differ from the genus *Cryptococcus* as follows:

(1) The vegetative cells have a flask-like appearance and do not show a well-marked double contour. (2) It has not been cultivated.

The genus *Pityrosporum* Sabouraud, 1895, contains two species, *Pityrosporum ovale* Bizzozzero, 1882, and *Pityrosporum cantliei* Castellani, 1908. Morphologically the fungus I have isolated is very similar. to *P. ovale*, but

it differs from it in the fact that it is of smaller dimensions and is cultivable, and, moreover, certain cells may show a double contour. In my opinion the fungus should be placed in the genus *Cryptococcus*.

Bacillus Vermiculoides Castellani, 1925.—This bacillus apparently lives in symbiosis with the *Cryptococcus* I have described; I have separated the two organisms with great difficulty, but I now have pure cultures of both. The bacillus is of rather large dimensions, its length varying between 2 and 6 microns; it is often curved in shape. It is Gram-positive, not acid-fast. The optimum temperature seems to be 37° C., but may grow, though much less abundantly, at much lower temperature—22° C. and even less.

Glucose Agar.—Minute colonies somewhat resembling those of certain streptococci.

Gelatin.—Growth very scanty or absent altogether, no liquefaction.

Serum.—No liquefaction of the medium.

Sugar Peptone Waters.—It produces acidity, but no gas in glucose, levulose, maltose, galactose, and lactose. There is usually no change in the other sugar-peptone waters.

Litmus Milk.—The medium is rendered acid and after a time may become clotted.

Biochemical Reactions of the Associated Organisms.—When glucose and levulose media are inoculated with a mixed cryptococcus-bacillus culture, acid and gas are produced, though slowly. The cryptococcus alone produces neither acidity nor gas, the bacillus alone produces only acidity.

MYCOTIC AFFECTIONS OF THE NERVOUS SYSTEM AND OF ORGANS OF SPECIAL SENSE

The mycotic affections of the central nervous system seem to be rare and are little known. Abscesses of the brain and cerebellum due to true actinomyces have been described by several authors.

In 1904, from the pus of a cerebellar abscess, I grew an extremely delicate fungus, a nocardia which was Gram-positive and partially acid-fast. No club-like formations were present in microscopic preparations. This nocardia grew comparatively well on sugar media, very slowly and scantily on ordinary agar. On all media the colonies had a black pigmentation. In cases of systemic infections due to saccharomyces, monilia, and endomyces-like fungi, abscesses containing such fungi may be found in the brain and spinal cord, as in other organs of the body. A meningitis due to yeast-like fungi has been described, an interesting case being put on record by Freeman and Weidman due to *Cryptococcus histolyticus* Stoddard and Cutler.

Organs of Special Sense.—Mycologic affections of the eye may be classified as follows: (1) Due to species of genus *Nocardia* and genus *Cohnistreptothrix, ocular nocardiasis.* (2) Due to various species of:

Genus *Saccharomyces*
Cryptococcus
Endomyces
} Ocular blastomycosis.

(3) Due to fungi of genus *Monilia,* ocular moniliasis.
(4) Due to fungi of genus *Oïdium,* ocular oïdiomycosis.
(5) Due to fungi of genus *Aspergillus* and *Penicillium,* ocular aspergillosis and pencilliosis.
(6) Due to fungi of genus *Sporotrichum,* ocular sporotrichosis.
(7) Due to fungi of genus *Glenospora,* ocular glenosporosis.
(8) Due to fungi which have not yet been classified.

A Mycosis Not Very Rare in the Tropics is Moniliasis.—I have seen several cases in Singhalese children of a conjunctivitis apparently due to monilia; the conjunctiva was highly inflamed, there were photophobia and purulent discharge. The microscopic examination showed, in addition to pus-cells, numerous yeast-like bodies. No gonococci or any other bacteria were present. Agar and various sugar-agar tubes were inoculated with the pus, and a monilia fungus was grown. It is to be noted that not rarely, at least in the tropics, spores of various fungi are found in the slight secretion which so often collects at the angles of the eyes even in normal people, but these spores do not, apparently, usually give rise to any symptoms.

Rhinomycosis.—Yeast-like and other fungi are often observed in the nasal mucus; they may play only a saprophytic rôle or they may give rise to an inflammation of the mucosa. They may give rise to a condition indistinguishable from hay-fever. In Colombo a little native boy was brought to me by his parents, who stated that he had been suffering for the last three months from repeated attacks of severe sneezing, and that they had observed that on blowing the nose minute black dots were coming out in the mucus. Microscopic and cultural investigations showed this case to be one of aspergillosis due to *Aspergillus niger.* In the literature cases of aspergillosis of the nose due to

A. glaucus (De Bary) and *A. fumigatus* (Fresenius) have also been described.

Otomycosis.—Various fungi may be present in the external auditory canal without causing any symptoms. In some cases, however, the fungus multiplies abundantly, and may be the cause of a local inflammation or may apparently facilitate the formation of a wax plug. In several cases I have found a monilia which I have called *Monilia rhoi* (see table of Monilias, p. 1128). In 2 cases of otomycosis I have found a fungus belonging to the family *Mucoraceæ*, *Lichteimia ramosa* (Lindt, 1886). It was present in great quantity, and the patient complained of tinnitus aurium and deafness. It is interesting to note that this fungus is found often in the nasal mucus of horses, and both of my cases were Tamil *muttus* (horse keepers). Various authors (Siebenmann, Boke, Huckel, etc.) have recorded cases due to *Lichteimia corymbifera* (Cohn), *Rhizomucor septatus* (von Bezold); Maggiora and Gradenigo found *Saccharomyces ellipsoides* (Rhees) in a case of chronic otitis media. The same authors found a new species of saccharomyces (*S. roseus*) in the eustachian tube.

Aspergillomycosis of the ear is comparatively frequent; I have seen several cases in Ceylon, apparently due to *Aspergillus fumigatus* (Fresenius); Cramer observed *A. niger* (von Tiegham); Wreden, *A. flavus* (De Bary); Siebenmann, *A. repens* (De Bary); and *A. nidulans* (Eidam). Fungi of the order *Basidiomycetes*, family *Ustilaginese*, have also been observed: *Ustilago carbo* and *Tilletia levis*. Of the order *Hyphomycetes*, *sensu stricto*, *Trichothecium roseum* (Persoon, 1901) has been observed in a few cases. In New Orleans otomycosis due to *Aspergillus* and other fungi is common, especially in colored people.

With regard to treatment I have found hydrogen peroxid 2 parts, alcohol 1 part, useful; some authorities recommend a 2 per cent. alcoholic solution of salicyclic acid, which, however, at times gives severe pain; Deeks has obtained excellent results from a 2 per cent. solution of mercurochrome.

BRONCHOMYCOSES

For some years I have endeavored to emphasize the importance and comparative frequency of bronchomycosis. In several publications I have attempted an etiologic classification of these affections and have given a botanical description and classification of the fungi found. Today I propose touching upon the subject solely from a practical standpoint, from the point of view of the clinician and clinical pathologist. Those interested in the botanical and mycologic details will find these in various publications of mine, and in Castellani and Chalmers' "Manual of Tropical Medicine," chapters on Fungi.

From a practical point of view Bronchomycoses may be classified as follows:

1. Due to "yeast-like fungi," viz., fungi of the type *Blastomyces, Cryptococcus, Saccharomyces, Monilia, Endomyces. Torula* is now generally considered a synonym for *Cryptococcus.*

2. Due to filamentous fungi: (*a*) Of the slender type, viz., fungi of the types *Nocardia, Anæromyces, Vibriothrix*; (*b*) of the larger size, *Oïdium, Hemispora;* (*c*) with characteristic conidial structures and fructifications, etc., *Aspergillus, Penicillium, Mucor, Rhizomucor, Acremoniella, Sporotrichum, Acladium.*

There are certain symptoms common to all bronchomycoses whatever fungus is the etiologic factor. In mild cases there are types of slight bronchitis with mucopurulent expectoration in which the fungi are found. In severe cases the patient presents symptoms suggesting phthisis with hectic fever and hemorrhagic expectoration. Most bronchomycoses are benefited by the administration of potassium iodid. The prognosis varies a great deal according to the causative fungus; the cases due to *Nocardia* have the worst prognosis.

BRONCHOMYCOSES DUE TO "YEAST-LIKE" FUNGI

By yeast-like fungi we understand fungi characterized by the presence in the lesions, and usually in cultures too, of numerous round or oval cells, some of which are budding; if mycelium is present, it is present in very small amount. Yeast-like fungi belong to very different botanical groups of mycetes, different genera, different families. From the point of view of the clinical pathologist the following types of yeast-like fungi may be distinguished: *Blastomyces* type, *Cryptococcus* type, *Monilia* type, *Saccharomyces* type, *Willia* type, *Endomyces* type.

Blastomyces.—In the lesions large round or oval cells are present with an exceedingly well-marked double contour, and protoplasm very granular. No mycelium in the lesions. Cultures may be fluffy (aëreal hyphæ) and contain a large amount of mycelium. Asci have been described by certain authors. These fungi do not produce gas fermentation in sugars.

Cryptococcus.—In the lesions round or oval cells are found smaller than Blastomyces. The cells have no double contour or only faint; the protoplasm is not granular or only slightly so. Neither in the lesions nor in cultures is mycelium present. These fungi do not produce gas fermentation in glucose or any other sugar.

Monilia.—As cryptococcus, but mycelium, although usually in exceedingly small amount, is present, either in the lesions or in cultures, or in both. No asci. These fungi often produce gas fermentation of various sugars (see table, p. 1128).

Saccharomyces.—As *Cryptococcus*, but asci and ascospores present. These fungi produce gas fermentation.

Endomyces.—As *Monilia*, but asci and ascospores present.

Willia.—Fungi of this type are characterized by the presence of asci with peculiarly shaped ascospores: so-called "bowler-hat" ascospores. The cultures have a pleasant fruity odor. These fungi do not produce alcoholic fermentation; they produce a fairly large amount of various ethers.

With regard to Bronchomycoses due to yeast-like organisms I will limit myself to touching very briefly on the following:

1. Broncho-moniliasis.
2. Broncho-blastomycosis.
3. Broncho-cryptococcosis.
4. Broncho-saccharomycetosis.
5. Broncho-williasis.
6. Broncho-endomycosis.

BRONCHO-MONILIASIS

Remarks.—I first called attention to this bronchial affection in Ceylon in 1905, and valuable work on the subject has been carried out recently by a number of authors: Chalmers and O'Connell, Farah, Mendelson, Macfie, Iacono, Tarkanath Sur,

F. M. Johns, Pollacci, Redaelli, Perin, Jockes and Simpson, etc. The condition, however, is still little known, though it has been found in many tropical and subtropical countries, and also in temperate zones.

Pinoy has described cases in France, Pijper in South Africa, Macfie in West Africa, and Chalmers and MacDonald and Farah have observed a number of cases in the Soudan and Egypt. Taraknath Sur has made a thorough study of the disease in India. Iacono has found several cases in the south of Italy, and cases have recently been found in England by Douglas, Thompson, and myself, and in America by Johns, Boggs and Pincoff, and Simon. The condition appears to be caused by several species of the genus *Monilia* Persoon, usually *M. tropicalis* Castellani, *M. pinoyi* Castellani, *M. krusei* Castellani, and *M. metalondinensis* Castellani.

Etiology.—As regards the botonical characters of the genus *Monilia*, the original definition by Persoon is "stipitata aut effusa byssoidea. Fila moniliformis articulata." These fungi are stated to be characterized by the sporophores being simple or subsimple, and producing by constriction at their extremities a chain of large lemon-shaped conidia, often provided with a disjunction apparatus. The general teadency at the present time, however, is to extend the term "Monilia" so as to include all those organisms of the family *Oösporaceæ* Saccardo, 1886, the vegetative body of which (Thallus) in its parasitic life (*in situ*, in the lesions) appears as a mass of mycelial threads and free budding forms, some of the mycelial filaments being long and branched, and of rather large size, and often presenting arthrospores. In the saprophytic life (cultures on the usual solid laboratory media) mostly yeast-like roundish or oval bodies are seen, while mycelial filaments are very scarce or absent, and when present they are rather short and consist only of a few articles. Monilia fungi very often ferment glucose and other carbohydrates, with production of gas.

For practical purposes Monilias may be conveniently classified according to some of their biochemical characteristics. The classification has been given when discussing thrush (p. 1128).

Inoculation Experiments in the Lower Animals.—In Ceylon I carried out a fairly large number of researches on the virulence of various Monilias and the experimental reproduction of broncho-moniliasis. More recently Douglas, Iacono, Mendelson, Redaelli, and others have worked on the subject in the tropics and also in England and Italy. The results of these researches may be condensed briefly as follows:

1. A few monilia strains are non-virulent. Their inoculation into rabbits and guinea-pigs by the subcutaneous, intravenous, intraperitoneal, intrapleural, intrapulmonary route does not kill either the rabbit or the guinea-pig, and the inoculated animals do not show any sign of sickness. These strains have generally been isolated from the air.

2. Certain monilia strains are virulent and kill the rabbit and guinea-pigs when inoculated intravenously or intrapulmonarily, but they do not produce any evident pseudotubercular nodular condition of the lungs.

3. Certain monilias when inoculated intrapulmonarily (and at times intravenously) produce a peculiar nodular condition of the lungs. For instance, if $\frac{1}{2}$ or 1 c.c. of a thick emulsion of *Monilia metalondinensis* Castellani strain C (isolated from a severe type of broncho-moniliasis) is injected intrapulmonarily in a rabbit through the thorax by means of a syringe and the animal is killed fifteen to twenty days after, the postmortem will show that both the lung which was injected and the lung which was not injected present numerous white nodules, which are generally larger in the inoculated lung. Some of these nodules may coalesce, forming a staphyloid mass. The invasion of the non-inoculated lung apparently is by the bronchi, which in many cases can be made out to be greatly expanded, and in some places their wall has given way. The histologic examination of the smaller nodules, which are about $\frac{1}{8}$ inch in diameter, shows that the center is composed of masses of small cells and polymorphonuclear leukocytes. Further out the cells are fewer in number. This corresponds to the area of the degenerating expanding bronchocele. Still further out there is a ring of endothelial cells; many of them are phagocytic, containing smaller white cells,

and there are a few large multinucleated giant-cells. There are also in this ring a large number of eosinophil cells. At times the cells in the center of the nodules are markedly degenerated, the nodules becoming caseous. Stained with Gram a section shows only a small number of monilia and few of the spores take the Gram stain. Between the nodules there is no pneumonia in most cases, but there is some congestion and there is considerable increase of endothelial cells. In the small arteries the intima is greatly thickened. The above histologic description is based on the researches carried out on the subject by Douglas, Thompson, and myself. The animal inoculations were performed by Douglas. The histologic lesions found in experimental moniliasis have been also thoroughly studied by Redaelli.

Symptomatology.—Clinically, a *mild type* and a severe type of the malady may be differentiated, with, of course, a number of intermediate cases. In the mild type the general condition of the patient is good and there is no fever. The expectoration is mucopurulent, often scanty, and does not contain blood. The physical examination of the chest is negative or reveals only a few râles. The condition may last for several weeks or months, or get cured spontaneously, or, continuing, may turn into the severe type.

The *severe type* closely resembles phthisis. The patient becomes emaciated, there is hectic fever, and the expectoration is often hemorrhagic and may at times have a peculiar "brewer's yeast" odor. The physical examination of the chest may show patches of dulness, fine crepitations, pleural rubbing. This type may end fatally.

The treatment consists in giving potassium iodid, with which glycerophosphates and balsamics may be associated. It is interesting to note, however, that in a certain number of cases potassium iodid has practically no beneficial action whatever. Vaccines are occasionally useful.

ILLUSTRATIVE CASES

Case I.—A. T. S., male, pensioner, born 1890, joined the British Army in 1914. While serving in 1916 noticed slight cough with scanty expectoration, but his general condition of health was fairly good. Ailment continued

till December, 1921, when the sputum began to be bloody and the patient began losing flesh. Weight in July, 1919 was 11 stones, 4 pounds; March, 1922, 9 stones, 9 pounds; June, 1922, 8 stones, 13 pounds.

He was suspected to be suffering from tuberculosis and was sent to the Ministry of Pensions Hospital, at Orpington, on March 31, 1922, for observation. His general condition of health was fairly good, but he was very thin. The patient had a slight serotine fever of low type, 99° to 99.4° F., not influenced by quinin. There were no regular sweats. The cough was more severe in the morning than at night. The examination of the chest did not reveal anything very definite. A few coarse râles were present; the *x*-ray examination did not show any evidence of tuberculous lesions. Complement deviation test for tuberculosis bacillus negative. Wassermann negative.

The sputum was examined for the tuberculosis bacillus many times—always negative. A fungus was grown with the characteristics of *Monilia metalondinensis* Castellani.

He was treated with potassium iodid and creosote, and all the symptoms disappeared. He was discharged from the hospital as cured, but we kept in touch with his family doctor, who wrote to us some months afterward that the patient was feeling well and was able to do a day's work.

Case II.—Col. A. S., while in India, developed symptoms of subacute bronchitis with mucopurulent expectoration and occasionally hemorrhage. He was diagnosed as a case of broncho-moniliasis and sent home. I was able to confirm the diagnosis. He got well on potassium iodid and creosote. In this case the Monilia was of the *pinoyi* type.

Diagnosis.—The diagnosis is based on the absence of the tubercle bacillus and the constant presence of Monilias in the sputum. It is essential that the sputum should be collected in sterile receptacles after the patient has gargled thoroughly with warm, sterile water, and the sputum should be examined immediately. In certain cases the microscopic examination of the sputum shows spore-like, roundish or oval cells, often presenting a double contour and occasionally some portions of mycelial threads. In other cases the microscopic examination is completely negative, and the fungus can be found only by cultural methods. At any rate, it is impossible to make a definite diagnosis of broncho-moniliasis without a cultural investigation, which should be carried out as follows:

A small amount of sputum is smeared on several tubes of glucose or maltose agar, which should be kept at a temperature of 22° to 25° C. for two or three days, when, in positive cases, white, rather large roundish colonies will appear, easily differentiated, as a rule, with a little practice, from the colonies of

cocci and other bacteria. To determine the species of Monilia present, the strain isolated should be further investigated by inoculating milk, gelatine, serum, and the following carbohydrates: glucose, levulose, maltose, galactose, saccharose, inulin, and dextrin; and animal inoculations in rabbits should also be performed to see whether the strain isolated is virulent or not, and whether it is capable of producing pulmonary lesions.

It is essential to remember that the mere presence of a monilia fungus in the sputum should never be considered sufficient to establish the diagnosis of broncho-moniliasis. When a monilia is found in a sputum collected with all due precautions to avoid external contaminations and examined at once, there are three possibilities:

1. The monilia, though present in the expectoration, is not virulent and not pathogenic, and lives saprophytically in the bronchi. In such an event the monilia inoculated intravenously into a rabbit will be found to be non-virulent, and when inoculation is intrapulmonary it will produce no lesions in the lungs and no general infection.

2. The monilia, though virulent, may represent only a secondary invader, a secondary infection; in this case the intravenous injection of the fungus will kill the rabbit; the intrapulmonary injection will not cause any localized nodular affection in the lungs. It will induce a general fungus septicemia from which the animal will die.

3. The monilia is the real cause of the broncho-alveolar condition; in such cases the intrapulmonary injection into a rabbit will produce a very characteristic nodular condition of the lungs. When the animal dies spontaneously or is killed, fifteen to twenty-one days after the intrapulmonary injection, both lungs (the one injected and the other in which no injection was made) are found to be studded with a large number of white nodules containing the fungus. These white nodules are about $\frac{1}{8}$ inch in diameter. In the intervening lung tissue there are signs of congestion, but no pneumonia.

The center of the small nodules is composed of small cells—polymorphic leukocytes—further out there is a ring of endothelial

cells, many of them phagocytic and containing smaller white cells; and there are a few large multinucleated giant-cells and a large number of eosinophil cells. The cells in the center of the nodule are markedly degenerated, and the nodule is becoming caseous. Sections stained by Gram stain show only a small number of monilias, and few of the spores take the Gram stain. Between the nodules there is some congestion, but no pneumonia, and there is a considerable increase of endothelial cells. In the small arteries the intima is greatly thickened. The invasion of the lung tissues (in the side not injected) apparently takes place through the bronchi. These can in many cases be made out to be greatly expanded, and in some places their wall has given way.

Primary and Secondary Broncho-moniliasis.—Primary broncho-moniliasis should be distinguished from secondary broncho-moniliasis, which fairly frequently develops in cases of tuberculosis and other chronic conditions, as shown by Chalmers, Macfie and Ingram, myself, and other observers. A diagnosis of primary broncho-moniliasis should be arrived at by using great caution, because:

First, monilia fungi are frequently very abundant in the air of tropical countries, and very quickly contaminate samples of sputa that by any chance have been exposed to the air, even for a few seconds.

Second, these fungi, especially in the tropics, are not rare in the mouth, in the saliva, and, therefore, a patient should be made to gargle and rinse his mouth with sterile salt solution before he is asked to cough and expectorate.

Third, even if the fungus be present in the mucus originating from the bronchi, there are apparently certain cases in which the fungus is not pathogenic, being merely a saprophytic organism.

A definite diagnosis of primary broncho-moniliasis, therefore, should be arrived at with great caution, when the bronchial expectoration collected with every precaution and examined at once contains a monilia, tubercle bacilli being absent, and the amount of the fungus present decreases rapidly with the gradual improvement of the condition. The monilia by intrapulmonary

injection in a rabbit should give rise to a diffuse nodular condition. Pathogenic monilias mostly belong to the following groups: *krusei*, *metalondinensis*, *pinoyi*, *tropicalis*. The monilia, as I have already stated, not only must be virulent to the rabbit by intravenous inoculation, but the intrapulmonary injections of it must induce in the rabbit lungs a nodular condition which later becomes caseous.

Mixed Infections.—Cases of apparently true mixed infection, as, for instance, broncho-moniliasis and broncho-spirochetosis, have been put on record by several observers.

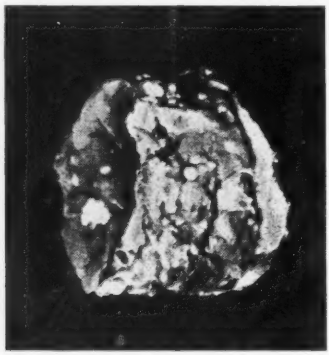

Fig. 183.—Experimental pulmonary moniliasis. Lungs of inoculated rabbit.

Prognosis.—The prognosis of true primary broncho-moniliasis must be reserved, as at times no treatment is of any avail, and the patient goes from bad to worse and finally dies.

Treatment.—Potassium iodid is useful in certain cases, but not in all. It is advisable to associate with it the administration of balsamics (principally creosote), and glycerophosphates. Monilia vaccines are useful in only a few cases.

Tea-taster's Cough.—In connection with broncho-moniliasis I might say a few words on the so-called "tea-taster's cough" and "tea-factory cough." In 1906 a young assistant in one of the big Ceylon firms, a tea-taster, came to consult me about a chronic cough, which he said had not yielded to ordinary treatment, and had been suspected by several medical men to be of

tuberculous origin. He emphatically stated, however, that he did not believe it was tuberculosis. "I am merely suffering," he said, "from tea-taster's cough," an expression I had never heard before. The general condition of the patient was good, and the physical examination of the chest revealed only a few coarse râles. The microscopic examination of the sputum was negative for tuberculosis; instead. I noticed microscopically some mycelial filaments and some yeast-like bodies. I inoculated several glucose-agar tubes, and I grew a monilia fungus which, at the time, I believed to be an endomyces.

How did this patient get infected? Tea-tasters, in order to judge of the quality of the various teas, not only taste infusions, but often fill their hands with the tea-leaves and bury their noses in them, sniffing them up; in this way a certain amount of tea-dust enters the nasal cavities.

Now, if one examines tea-dust in Ceylon, one finds that it contains fungi of the genus Monilia constantly, of the genera Aspergillus and Penicillium frequently, and of the genus Oïdium occasionally. A peculiar streptococcus is also very often present. The same organisms are not rarely found in the nasal cavities of tea-tasters, and when bronchial symptoms appear in them monilia-like fungi are present in the expectoration. It is probable, therefore, that the so-called tea-taster's cough is a moniliasis, especially as a guinea-pig, in the nostrils of which I insufflated tea-dust regularly, died with symptoms of chronic bronchopneumonia.

What I have said about "tea-taster's cough" applies to a great extent to the so-called "tea-factory cough." For many years planters have noted in Ceylon that the coolies doing work in tea-factories, where the leaves are dried and there is a large amount of tea-dust floating about, after some months become weak, lose flesh, and often have a cough with mucopurulent expectoration. The planters have found by experience that these coolies must be taken away from the factory and sent to work in the field, and then the symptoms slowly disappear. I have examined some of these coolies, and their expectoration practically always contains fungi of the genus Monilia. I have

little doubt, therefore, that the so-called "tea-factory cough" is a bronchomycosis, and probably a broncho-moniliasis.

BRONCHO-BLASTOMYCOSIS
(Pulmonary Blastomycosis)

Remarks.—The term broncho-blastomycosis or pulmonary blastomycosis is now usually limited to indicate cases of bronchitis and broncho-alveolitis due to fungi of the type "Blastomyces," the same fungi which cause Blastomycosis cutis. In the past the term was often used to cover all pulmonary and bronchial conditions associated with presence of any kind of yeast-like fungi. The genus Blastomyces is not considered valid by most authorities, but it is useful to retain it from the point of view of the practical clinical pathologist.

Etiology.—The fungi found belong to the type blastomyces. In the lesions these fungi appear as large globular cells 7 to 20 microns with markedly granular protoplasm and a hyaline capsule which possesses a strikingly well-defined double contour, much more marked and defined than in monilias, saccharomyces, and ordinary cryptococcus in which the double contour may be lacking altogether or is not so visible. When the fungus is grown in glucose agar growth slowly develops with abundant white duvet; preparations from glucose-agar cultures show a large amount of mycelial elements.

Pathology.—The pathologic lesions resemble those of tuberculosis. The lungs may be seen to be studded with numerous white nodules. The cut surface may show a purulent fluid and cheesey material may be expressed from the involved region. Cavities of various size may be present.

The histologic structure of the lesions is somewhat similar to what one sees in tuberculosis; the central necrotic area is bounded by a zone of granulation tissue in which giant-cells are found; some of the giant-cells may contain blastomyces.

Symptomatology.—The patient complains of chronic cough with expectoration which is mucopurulent, and at times hemorrhagic. The general condition is poor, the patient steadily loses weight; there may be serotine fever.

The physical examination reveals signs of bronchitis and in advanced cases the signs are those of consolidation.

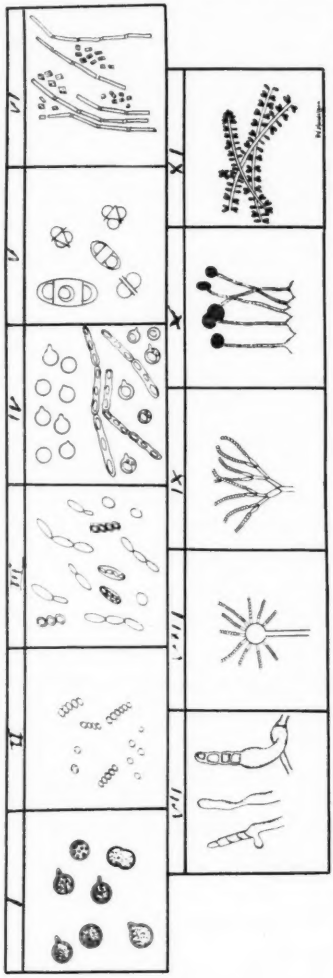

Fig. 184.—I. Blastomyces. II. Cryptococcus. III. Saccharomyces. Note asci with four ascospores each. IV. Monilia. V. Willia. VI. Oidium. VII. Hemispores. VIII. Aspergillus. IX. Penicillium. X. Mucor. XI. Sporotrichum.

The course of the malady is chronic and death is in most cases due to systemic infection.

Diagnosis.—The diagnosis is based on the presence in the sputum of the typical blastomyces cells: large round bodies with an exceedingly well-marked double contour, and markedly granular protoplasm; the blastomyces cells have usually a more marked granular protoplasm, a much more definite double contour, and are of larger size than monilia cells, saccharomyces cells, and the usual cryptococci.

In most cases typical blastomycetic lesions are found on the skin, elevated patches with papillomatous surface and well-defined margin; the presence of the skin lesions greatly facilitates the diagnosis.

Treatment.—This consists of giving potassium iodid in large doses, but unfortunately in most cases only a temporary improvement, not a cure, is obtained.

BRONCHO-CRYPTOCOCCOSIS

Symptoms identical with those found in broncho-moniliasis, but the causative fungi found belong to the genus cryptococcus. These fungi consist of numerous yeast-like, budding cells with no mycelium; cultures never present asci—this is the only characteristic that differentiates them from true saccharomyces. There are a primary and a secondary type of broncho-cryptococcosis. The treatment is the same as for broncho-moniliasis.

BRONCHO-ENDOMYCOSIS

This is caused by fungi morphologically identical with Monilia, but old cultures show presence of asci. It is a rare condition. The symptoms and the treatment are the same as for broncho-moniliasis.

BRONCHO-SACCHAROMYCETOSIS

This condition is caused by fungi of the genus Saccharomyces and other genera of the family of Saccharomyceteæ. These fungi are characterized from a practical point of view by the following features:

1. Reproduction by budding.
2. Absence of mycelium.
3. Presence of asci in old cultures.
4. Gas fermentations of one or more sugars. Symptomatology and treatment as in broncho-moniliasis.

BRONCHO-WILLIASIS

This is a very rare type of broncho-mycosis. The fungi found belong to the genus *Willia*. They are characterized by the peculiarly shaped ascospores, bowler-hat-like, etc. I have had one such case. The patient, a retired planter, got well on potassium iodid. The symptoms were the same as those found in chronic broncho-moniliasis.

BRONCHO-NOCARDIASIS

Broncho-nocardiasis is the modern term used to denote all bronchial and bronchopulmonary affections due to fungi of the genus *Nocardia*, Toni and Trevisan, and the genus *Cohnistreptothrix* Pinoy, which were previously more commonly known as *Streptothrix*, *Actinomyces*, *Discomyces*, *Oöspora*.

Two types of broncho-nocardiasis may be separated. One is characterized by the presence of fungal granules (sclerotia) in the sputum—granular broncho-nocardiasis.

In the other type no such granules are present—Agranular broncho-nocardiasis. The first type is still often referred to as Actinomycosis bronchialis or pulmonalis, and the second type as Pseudo-actinomycosis bronchialis or pseudo-actinomycosis pulmonalis. Before proceeding with the subject it may be of advantage to give a few botanical data on the nocardial fungi. These fungi belong to the order *Microsiphonales*. This order is characterized by the mucelium being composed of fine bacilliform hyphæ, usually 1 micron or less in diameter. They are, as a rule, Gram-positive when young, and without distinct nuclei; they are parasitic or saprophytic. Some species are acid-fast.

The order *Microsiphonales* has the following families:

A. *Nocardiaceas* Castellani and Chalmers, 1918 (Synonyms, *Actinomycetes* Lachner-Sandoval, 1898; *Trichomycetes* Petrusky, 1903).

Definition.—*Microsiphonales* with a mycelium.

Type Genus.—*Nocardia* Toni and Trevisan, 1889.

B. Mycobacteriaceæ Miche, 1909.

Definition.—*Microsiphonales* without a mycelium.

Genus 1. *Mycobacterium* Lehmann and Neumann, with the diphtheria bacillus as a type.

Genus 2. *Corynebacterium* Lehmann and Neumann, with the tubercle bacillus as type.

FAMILY NOCARDIACEÆ

Synonyms.—*Actinomycetes* Lachner-Sandoval, 1898; *Trichomycetes*, Petrusky, 1903.

Definition.—*Microsiphonales* with a mycelium.

Type Genus.—*Nocardia* Toni and Trevisan, 1889.

Classification.—This family contains 2 genera:

A. Grows aërobically, easy of cultivation, and producing arthrospores. Genus 1, *Nocardia* Toni and Trevisan, 1899.

B. Grows best anaërobically, but can at times grow aërobically, difficult of culture and not producing arthrospores. Genus 2, *Cohni-streptothrix* Pinoy, 1911.

The reader interested in mycology may find further particulars on these fungi in Castellani and Chalmers' "Manual of Tropical Medicine," 3d ed., pp. 1040–1062.

AGRANULAR BRONCHO-NOCARDIASIS

(Broncho-streptothriocosis, Pseudo-actinomycosis)

This is one of the most serious types of bronchomycosis. It generally runs a chronic course, although occasionally acute cases are met with. The patient loses flesh, becomes anemic, often has serotine fever; expectoration is at first mucopurulent, later tinged with blood; true hemoptysis may occur. The physical examination of the chest may reveal patches of dulness, crepitations, and pleural rubbing; occasionally, however, the physical examination will reveal nothing at all.

The microscopic and cultural examination of the sputum is most important, segments of thin, bacillary fungi will often be found, branching, at times acid-fast, at times not acid-fast, but Gram-positive. Aërobic and anaërobic methods of cultivation should be used, as some nocardias (cohnistreptothrix) grow only anaërobically.

The treatment of these cases consists of giving potassium iodid in large doses internally and autogenous nocardia-vaccines by hypodermic injection. Occasionally this mixed treatment gives good results, but in my experience most cases do not answer to this or any other treatment I know of, and end in death.

GRANULAR BRONCHO-NOCARDIASIS

(Broncho-actinomycosis)

The clinical symptoms are very similar to those observed in agranular broncho-nocardiasis, but the sputum contains small granules composed of an enormous number of thin mycelial fila-

ments, mixed with some débris. This type of nocardiasis is more amenable to treatment than the agranular type, and potassium iodid in large doses is fairly frequently successful.

ILLUSTRATIVE CASES

(Agranular Broncho-nocardiasis)

Case I.—European, male, thirty-two years of age, a planter in various tropical countries during the last twelve years. Two years ago he began complaining of slight cough, with very little expectoration. The physical examination of the chest revealed little, apart from a slight diminution of resonance in the left supraclavicular region. Cuti reaction negative.

The sputum was examined twelve times for tubercular bacillus, with constantly negative results. Instead a branching, Gram-positive, partially acid-fast organism was present, which I succeeded in growing. A protracted course of potassium iodid treatment, combined with the subcutaneous administration of autogenous vaccine, prepared with the fungus, was very successful.

Case II.—This is a most interesting case investigated at St. John's Hospital by Dr. Woodward, who has kindly allowed me to quote it and has supplied me with the following notes:

Captain served through the war, and after demobilization went to Rhodesia, where he had previously resided. In the early summer of 1922 he began to feel unwell and showed loss of weight, and had a cough and some expectoration. A few weeks after this he started to come home on leave to England, and the condition progressed. On his arrival in England he came to see me and told me this history: He had lost a considerable amount of weight and brought up sputum that at times was blood stained. He looked very ill, and appeared to be in a condition of rapid phthisis. On examining a direct smear of his sputum I found it full of a network of branching rods, showing numerous ramifications, being acid-fast with Ziehl-Nielsson stain. He had an even temperature for some little time, which varied from 100° to 101° F. Shortly after this he went under the care of a physician, who tried all sorts of treatment of a medicinal nature without its having the slightest effect on the condition.

My findings of nocardia (streptothrix) was confirmed in July last year by Dr. Benians, who inoculated a guinea-pig intravenously. The animal showed considerable wasting, and was killed on the sixteenth day. Multiple nodules were scattered throughout the viscera. In August, 1922 specimens of the sputum were sent to me periodically, always showing the same microscopic picture. Owing to the presence of pyorrhea in the patient I was asked to examine his gums. I did not find the nocardia, but there were spirochetes very largely mingled with fusiform bacilli.

In November there appeared two pyemic abscesses—one in the neck and the other in the side. I examined the pus from both of these places, and in direct smears they both showed the streptothrix to be present in very large quantities. No other organism was seen, nor was there any growth obtained of any other organism.

He died in the month of November, 1922.

I find that the organism was markedly acid-fast with Ziehl-Nielsson stain, but after keeping, the color tended to disappear. It was Gram-positive, and showed distinct variations of staining inside the rods. The organism from the sputum was at first anaërobic, and I grew it in a glucose broth. Later, when I obtained the organism from the pus, it was aërobic and anaërobic, and grew very much more easily on any media than when I had obtained cultures from the sputum. It showed a white, flowery looking growth. I gave intraperitoneal inoculation into a guniea-pig and it died on the eighth day.

GRANULAR BRONCHO-NOCARDIASIS

Case I.—A Serbian soldier, aged twenty-three, presented all the usual symptoms of pulmonary tuberculosis—great loss of flesh, serotine fever, bloody expectoration. The physical examination of the chest revealed patches of dulness with crepitations and pleural rubbings. The sputum was mucopurulent, occasionally tinged with blood. It contained at times some very small whitish granules the size of a pin-head, composed of an enormous number of thin, mycelial filaments, branching, Gram-positive, and partly acid-fast. The fungus grew fairly well aërobically on maltose and glucose agar. The colonies developed slowly, were hard, and firmly attached to the medium. They were of a pinkish color, and gelatin was slowly liquefied. Potassium iodid was administered in large doses and also hypodermic injections of an autogenous nocardial vaccine, but without any marked beneficial result.

Case II.—Young Indian student, twenty years of age. His medical attendant sent him to me, as he suspected tuberculosis, but he could never find the tuberculosis bacillus in the sputum. The patient was very thin and had serotine fever and sweatings; he coughed a great deal; the expectoration was at times mucopurulent, at times hemorrhagic. I had him cough, in my presence, into a sterile Petri-dish, and in the sputum, which was mucopurulent, I noticed several minute, yellowish bodies or granules, which the microscopic examination revealed as composed of thin mycelial elements, Gram-positive, but not acid-fast. I grew the fungus with great difficulty. Potassium iodid in very large doses (gr. xxx three times a day) without any vaccine had an almost wonderful effect; within five weeks all the symptoms disappeared.

BRONCHO-ANAËROMYCOSIS

This mycosis has been investigated by Douglas, Thompson, and myself. We have given, temporarily, the generic name *Anaëromyces* to a group of bacillary fungi of the order *Microsiphonales* Vuillemin, 1912, which are found in certain cases of bronchitis, and which show transition and intermediate characters between the genus *Corynebacterium* Lehmann and Neumann, 1896, the genus *Mycobacterium* Lehmann and Neumann, 1896, and the genus *Nocardia* Toni and Trevisan, 1889 (*Cohnistreptothrix* Pinoy, 1911, *pro parte*), of the family *Nocardiaceæ* Castellani and Chalmers, 1819 (*Actinomycetes* Lachner-Sandoval, *Trichomycetes* Petrusky).

The organisms of this group, *Anaëromyces*, are very closely related to the genus *Corynebacterium* Lehmann and Neumann (diphtheria and diphtheroid bacilli), and the genus *Nocardia* Toni and Trevisan (*Actinomyces* Harz, *Discomyces* Rivolta, *Streptothrix* Rossi-Doria, *Oöspora* Sauvageau and Radias, *Cohnistreptothrix* Pinoy, *pro parte*), but, in contrast to the former, branching is much more marked, and they are strictly anaërobic;

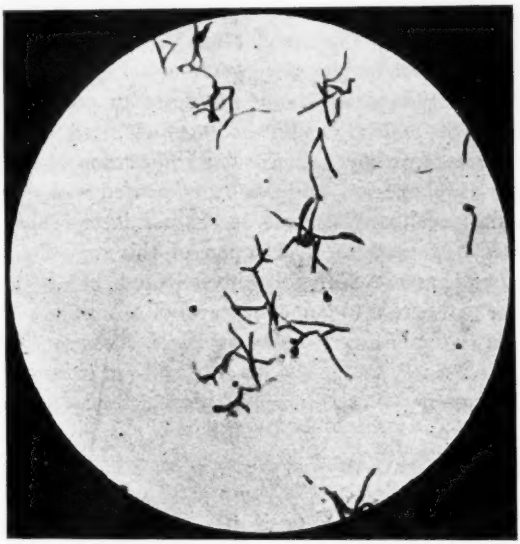

Fig. 185.—Anaëromyces bronchitica (Castellani, Douglas, and Thompson).

and, in contrast to the latter, the mycelium is very much less developed, the growth is moist and not dry and crinkled, and they never give rise to actinomitic granules in the lesions. They are Gram-positive, non-motile, and not acid-fast. These germs or similar ones were found in cases of bronchitis in 1904 by Chalmers and myself, and were referred to in a short paper read at the time as "Bronchial Anaërobic Diphtheroid Bacilli," but the observation attracted very little notice. They are also somewhat similar to *Bacillus Vitulorum* Flügge.

Anaëromyces bronchitica Castellani, Douglas, and Thompson. —*Morphologic and Staining Characteristics.*—The organism is bacillus-like and resembles in its shape a diphtheroid bacillus, but branching is much more marked. It is Gram-positive and not acid-fast. It measures 3 to 5 microns in length and 0.3 micron in breadth.

Motility.—The organism is non-motile.

Relation to Oxygen.—The organism is an obligate anaërobe.

Cultural Characters.—Provided a strictly anaërobic technic be used, the germ grows well in glucose agar and other laboratory media. The growth on glucose agar and other media is not very characteristic. The fungus does not seem to grow in gelatin at 22° C.

Biochemical Reactions.—There is no formation of acidity or gas in any carbohydrate we have experimented with, viz., glucose, levulose, maltose, galactose, saccharose, lactose, and inulin.

Animal Experiments.—The action of this organism in the lower animal has not been fully investigated, but it does not seem to be pathogenic to guinea-pigs, rabbits, or mice.

Pathologic Conditions in Man in which Anaëromyces Bronchitica Has Been Found.—The fungus has been isolated from a fairly large number of cases of bronchitis which may be classified into two groups:

The hemorrhagic type.

The mucopurulent type.

Cases of hemorrhagic type closely resemble pulmonary tuberculosis; there may be intermittent or remittent fever; the patient may become anemic and lose flesh; the expectoration contains blood and is at times of very characteristic bright brick-red color. The physical examination of the chest may be at times almost completely negative; at other times it may show signs, such as patches of dulness and crepitations, pointing to tuberculosis.

The symptoms noted in mucopurulent type do not differ from those of an ordinary case of subacute or chronic bronchitis. The sputum is mucopurulent or at times purulent; there may be slight fever, but the general condition of the patient is not af-

fected for a long time. In some cases the mucopurulent type, after a variable period of time, turns into the hemorrhagic type.

Geographic Distribution.—The organism has been found in cases which contracted the disease in Ceylon, in the Federated Malay States, Serbia, Italy, France, and England.

Mixed Infection.—The organism has been grown occasionally from bronchial cases in which Monilia and other fungi, and also the tubercle bacillus, were present.

Pathogenicity of Anaëromyces.—The animal experiments carried out by Douglas do not seem to show that the germ causes any very serious lesion in guinea-pigs, rabbits, or mice, and this is, of course, an argument against the organism's being pathogenic. On the other hand, the following facts are in favor of its pathogenicity to man: (1) The anaëromyces present in the sputum rapidly decrease in amount, and finally disappear with the gradual improvement of the bronchial condition; and (2) in a number of cases the hemorrhagic expectoration very rapidly ceases and all the symptoms quickly disappear, when an anaëromyces vaccine is used without any other treatment. It is, therefore, probable that anaëromyces has at least some part in the etiology of certain cases of hemorrhagic bronchitis.

Broncho-vibriothrixosis

Fungi of the type *Vibriothrix* have been found in certain cases of chronic bronchitis, but it has not yet been established whether these fungi are pathogenic.

Broncho-oïdiosis

This is clinically identical to Broncho-moniliasis, and, as in the case with Broncho-moniliasis, a primary and a secondary form should be distinguished. The fungi belong to the genus *Oïdium sensu* Pinoy, and are characterized by abundant mycelium with numerous arthrospores, but, in contrast to Monilia, free yeast-like budding cells are absent or rare. They may produce acidity in various sugars and other carbohydrates, but never gas. This genus (*sensu* Pinoy) contains 4 principal species:

O. lactis Link, 1908.

O. rotundatum Castellani, 1911.

O. asteroides Castellani, 1914.

O. matalense Castellani, 1915.

They may be differentiated as follows:

1. Surface of the culture smooth or only very slightly crinkled, produces acidity in glucose, though not constantly, but in no other carbohydrates. *O. lactis.*

2. Surface with duvet, produces no acidity or only very slight in the usual carbohydrates. *O. matalense.*

3. Surface vermiform, acidity in glucose, levulose, galactose, maltose, and lactose. *O. rotundatum.*

4. Colonies with peculiar radiating appearance. *O. asteroides.*

The reader interested in mycology may find further details regarding these fungi in Castellani and Chalmers' "Manual of Tropical Medicine," 3d edition, page 1903.

Broncho-hemisporosis

This condition, first described in 1910 by me, in Ceylon, is due to fungi of the genus *Hemispora* Vuillemin, which are characterized by the conidiophores terminating in an ampulliform structure with formation of Protoconidia and Deuteroconidia. The species which have so far been isolated are two, one identical to *H. rugosa* Castellani, previously found in the tropics, and the other probably a new species or at least variety, *Hemispora pararugosa* Castellani, Douglas, and Thompson. The principal characters of these two fungi are, briefly, the following:

Hemispora rugosa Castellani, 1910 (synonyms, *Monilia rugosa* Castellani, 1910), is a hyphomycete with the botanical characters of the genus *Hemispora;* is Gram-positive, but not acid-fast; the growth on glucose agar is abundant with a crinkled surface, occasionally ceribriform, and amber yellow or brownish color. No gas is produced in any sugar, but a little acidity may be present in glucose, levulose, saccharose, and maltose. The fungus usually has no action on milk, but occasionally it induces a slight degree of peptonization with a small coagulum at the bottom of the tube. Gelatin is very slowly liquefied. This fungus was first found by me in cases of bronchitis and tonsillitis,

in Ceylon, and later by Pijper in certain cases of thrush. I at first placed the fungus temporarily in the genus *Monilia*, later removing it, at the suggestion of Professor Pinoy, to the genus *Hemispora*.

Hemispora pararugosa Castellani, Douglas, and Thompson, 1921, is morphologically and culturally very similar to *H. rugosa*. It is Gram-positive, but not acid-fast. It does not produce gas or acid in the usual sugars and carbohydrates, but at times produces acidity in starch. It does not liquefy gelatin, and there is no production of acid or clot in milk.

Symptomatology.—A mild and a severe type of the affection can be distinguished. In the mild type the general condition of the patient is good, there is no fever, and he simply complains of cough. The expectoration is mucopurulent and does not contain blood. The physical examination of the chest is negative, or only reveals a few coarse râles.

The severe type closely resembles phthisis: the patient becomes emaciated, there is hectic fever, and the expectoration may be bloody. The physical examination may reveal patches of dulness, fine crepitation, and pleural rubbing. It is interesting to note that the affection occasionally develops after a tonsillitis caused by the same fungi, and characterized by the presence of yellowish or grayish patches.

Treatment.—Potassium iodid in large doses generally answers well.

Broncho-endomycosis

This is caused by fungi morphologically identical with Monilia, but old cultures show presence of asci. It is a rare condition. The symptoms and the treatment are the same as for Broncho-moniliasis.

Bronchial Aspergillosis

This affection, known also as broncho-aspergillomycosis, pseudo-tuberculosis, aspergillus pneumomycosis, and in France maladie des gaveurs des pigeons (pigeon-breeders), is caused by fungi of the genus *Aspergillus* Micheli and *Sterigmatocystis* Cramer. These fungi are easily recognized by their very char-

acteristic fructifications: the conidiophore terminates into an ovoid or roundish formation, from which take origin numerous elongated claveiform elements, each of which supports a chain of roundish conidia. These fungi are generally saprophytes, but occasionally become true parasites. They grow quite easily in both acid and alkaline media. It is interesting to note that iron and manganese have a favorable influence on their growth and sporulation. When growing parasitically in the tissues of men and animals they often lose some of their characters and the typical fructifications are often absent, only mycelial segments and yeast-like cells being seen.

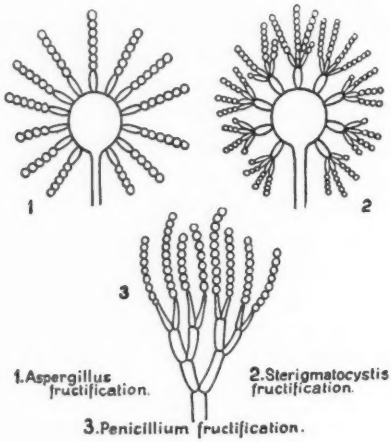

Fig. 186.

The classification of *Aspergillus* is difficult. In practice the principal types may be different, as follows:

1. Conidia, of very large size (9 to 15 microns in diameter), yellow, or reddish yellow, or gold-brown. *A. herbariorum* Wiggers.

2. Similar to herbariorum in general characteristics, yellow or yellow-green, but conidia somewhat smaller, though still large (7 to 8 microns). *A. repens* De Bary.

3. Similar to above two as regards color and being yellow

or greenish yellow, but spores smaller (5 to 7 microns in diameter) and with a granular surface. *A. flavus* De Bary.

4. On solid media, brownish black if the medium is alkaline or neutral, greenish if the medium is acid; conidia small (2 to 3 microns) and smooth. *A. fumigatus* Fresenius 1775.

Symptomatology.—There are signs of mucopurulent bronchitis. In severe cases hemoptysis may occur and there may be serotine fever. The disease often terminates fatally, and at the postmortem numerous mycotic nodules may be found in the lungs and occasionally in the liver and kidneys and other organs. Care should be taken to distinguish secondary Aspergillosis from primary Aspergillosis. Secondary Aspergillosis occasionally develops in tuberculosis, and not very rarely in gangrene of the lungs.

Diagnosis.—This is based on the mycologic investigation of the sputum. It is important to note that, as a rule, in the sputum only conidial elements and mycelial elements are seen microscopically.

Treatment.—This is difficult. Potassium iodid is useful in incipient cases, and a change of climate and occupation should be recommended.

Broncho-penicilliosis

The condition is clinically identical to broncho-aspergillosis, but the causative fungi belong to the genus *Penicillium* Link. Fungi of this genus are characterized by their fructifications, the whole fruit-bearing hypha with its sterigmata and conidia resembling a hair-pencil (Penicillium—hair pencil). The species most frequently found in man is *P. crustaceum* Linnæus (synonyms *P. glaucum* Linnæus, *Monilia digitata* Persoon). It is often found living saprophytically on bread, cheese, and fruits. The conidia are spherical, smooth, of a maximum diameter of 4 microns.

In Macedonia, during the World War, a Serbian soldier was sent to the hospital to which I was attached, with the diagnosis of pulmonary tuberculosis. He had been wasting for two months, and had serotine fever. Expectoration mucopurulent,

at times bloody. Repeated examination for tuberculosis negative. A few mycelial threads present. A fungus was grown with the characters of a Penicillium, probably P. crustaceum. Potassium iodid in full doses acted well.

Broncho-mucormycosis

This term is used to designate bronchial and bronchial-alveolar affections associated with fungi of the genus mucor Micheli, 1729, and the following genera:

Lichtheimia Vuillemin, 1904.

Rhizomucor Lucet and Constantin.

Rhizopus, Ehrenberg.

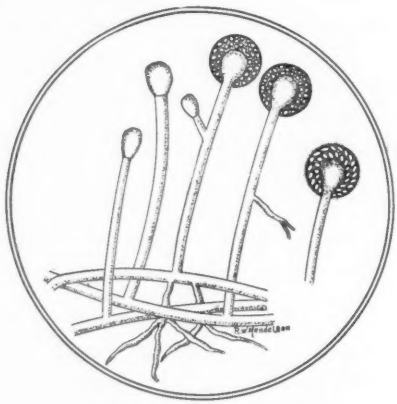

Fig. 187.—Rhizomucor.

These genera belong to the family *Mucoraceæ*, the members of which are characterized principally by the following features: Aërial hyphæ are present (gonidiophores) each of which supports on its distal extremity a pear-shaped globular or claviform formation, the sporangium or gonidiangium, which is at first separated from the gonidiophore by a septum. The septum later protrudes into the lower part of the sporangium to form a variously shaped structure called columella.

Inside the sporangium gonidia (Endospores) develop by free cell formation. Part of the sporangial protoplasm not used

in the formation of the endospores becomes transformed into a peculiar mucilaginous substance, which, at a later period, becoming swollen by absorption of water, causes the bursting of the sporangium. Each endospore or gonidium which has become free in this way gives rise to a mycelial tube by germination. The mycelial tubes ramify, and an abundant mycelium is produced.

In some species a form of partial sexual reproduction takes place by a process of zygosporosis, or conjugation of two gametes,

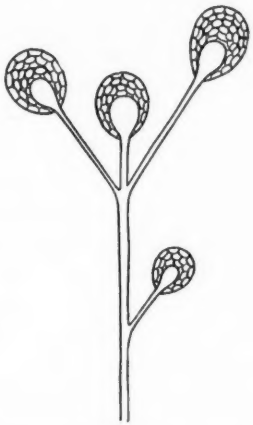

Fig. 188.—Rhizomucor parasiticus Lucet and Constantin.

which morphologically are not of different shape or structure, that is to say, they are not sexually differentiated. It must be noted that many species, when growing in unfavorable media, reproduce only by conidia. They require plenty of oxygen, and therefore the media tubes must never be closed with rubber caps; otherwise they lose their characteristics and grow monilia-like or yeast-like. The family *Mucoraceæ* may, from a practical point of view, be classified as follows:

1. Mycelium ramified, no rhyzoids (root-like hairs by which the plant is attached to the medium). *Mucor* Micheli, 1729.

2. Mycelium, non-ramified, with or without rhyzoids, spor-

angium terminates in a special formation, encircling the base of the columella. *Lichtheimia* Vuillemin, 1904.

3. Mycelium provided with rhyzoids columella ovoid. *Rhyzomucor* Lucet and Constantin, 1900.

4. Mycelium provided with rhyzoids columella, hemispheric, mushroom-like. *Rhizopus* Ehrenberg, 1820.

For further particulars on the botanical classification of these fungi, the reader may consult Castellani and Chalmers' "Manual of Tropical Medicine," 3d edition, pages 972–977.

Illustrative Case.—During the World War, while I was in the Balkans, in 1917, a Serbian soldier was sent to me with the diagnosis of pulmonary tuberculosis. He was losing flesh rapidly and felt very weak. Slight fever at night, a fair amount of expectoration, generally mucopurulent. The physical examination of the chest revealed nothing except a few coarse râles. Microscopic examination of the sputum for tuberculosis constantly negative; instead, a few segments of mycelium were noticed on several occasions; glucose-agar tubes and other media were inoculated, and a fungus was isolated which at first showed the characters of a monilia; in subcultures, however, the characteristic features of a mucor appeared with presence of the globular sporangia (columella), 5 microns in diameter, of yellowish color, spores elliptical, smooth. In what way did this man get infected? He was in charge of horses and often had to remove the horse dung, and, as is well known, horse dung almost always contains mucor.

Broncho-acremoniellasis

In a case at first considered to be a broncho-aspergillosis Perin isolated a fungus which was investigated by Pollacci. In glucose agar it produces a growth which is at first whitish, but later soon becomes black. The microscopic examination of the cultures shows abundant septate mycelium, the hyphæ being 3.5 to 4 microns in breadth. Each conidiosphore bears a terminal round spore 7.7 to 9.7 μ. in diameter, of a dark brown color. Pollacci considers the fungus to belong to the genus *Acremoniella* and has called it *Acremoniella perini*. Broncho-acremoniellasis clinically is identical with broncho-aspergillosis.

BRONCHO-CLADOSPORIOSIS

From a case of chronic bronchitis with occasionally hemorrhagic sputum I have isolated a fungus very similar to *Cladosporium mansoni* Castellani, which is the cause of Tinea nigra. Potassium iodid answered well.

BRONCHO-ACLADIOSIS

From 2 cases of chronic hemorrhagic bronchitis I have isolated a fungus which does not seem to differ in any important point from *Acladium castellanii* Pinoy, which is the cause of a peculiar ulcerative condition of the skin. The two cases got well on potassium iodid.

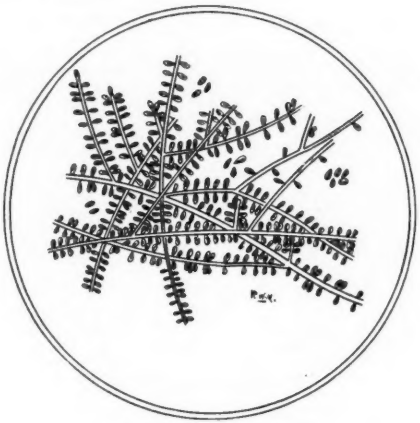

Fig. 189.—Sporotrichum.

BRONCHO-SPOROTHRICOSIS

In cases of dermal sporothricosis the fungus may occasionally attack the bronchi and the pulmonary tissues. But there is also, though it is rare, a primary broncho-sporothricosis. The patient has the symptoms of severe bronchitis or bronchopneumonia, with mucopurulent expectoration, occasionally tinged with blood. The diagnosis is based on the microscopic and cultural examination of the sputum. The microscopic ex-

amination will show presence of yeast-like bodies in certain cases, in others it will be completely negative. The sputum should be inoculated into several tubes of maltose agar, and left at room temperature for several days. In positive cases whitish colonies generally appear, which soon coalesce, forming a whitish cerebriform mass, and this later on becomes black or brownish. For the determination of species hanging-drop cultures may be prepared, and also cultures on various media, etc. The classification is based principally on the size and shape of the conidia, and may be found in the chapters on fungi in Castellani and Chalmers' "Manual of Tropical Medicine."

The prognosis is quite favorable, provided a correct diagnosis is made at an early stage. Potassium iodid in large doses is a specific.

CERTAIN MYCOSES OF THE GENITO-URINARY SYSTEM (URETHROMYCOSES, MYCOTIC BALANITIS, MYCOTIC VAGINITES)

Mycotic Urethrites.—These urethrites may be classified as follows:

1. Discharge whitish or yellowish.
2. Discharge dark brownish or greenish black or black.
3. Discharge reddish or pinkish.

1. **Mycotic Urethritis with Whitish or Yellowish Discharge.**—This condition is not very rare. I have seen several cases in the tropics and a few cases in the Balkans and in Southern Europe. I have also seen 3 cases in this country probably of the same nature. The discharge is generally present in very small amount and is of a whitish or yellowish color, but occasionally may be fairly abundant and closely resemble gonorrheal urethritis. The fungi found generally belong to the following genera: Monilia, Cryptococcus, Oïdium, Saccharomyces, Nocardia.

In Ceylon I noted the condition—due to a Monilia—in several cases of diabetes; in these cases the Monilia may affect not only the urethra but also the glans penis and corona; in some cases the glans and corona are affected, but not the urethra.

Illustrative Case.—A young Serbian officer in Macedonia consulted me for a fairly abundant purulent urethral discharge.

He was greatly distressed; he was engaged and believed he was suffering from gonorrhea, though he denied having exposed himself to infection. I examined the secretion; no gonococci present; instead, a very large number of yeast-like cells and a few mycelial segments could be seen. The cultural investigation showed presence of a monilia very similar to *M. krusei*. I prescribed a mixture containing potassium iodid, sodium bicarbonate, glycerin, syrup of tolu, and irrigations with a solution of perchlorid of mercury 1 : 20,000. The discharge disappeared completely within ten days.

2. **Black Mycotic Urethritis.**—This is an exceedingly rare condition. I have seen cases in the Tropics and in Southern Europe. The discharge is present in very small amount and is usually blackish, greenish black, or brownish. In certain cases minute granules may be present, which, on microscopic examination, are seen to consist of mycelial threads and spore-like bodies. The fungi found generally belong to the following genera: Cladosporium, Aspergillus, Penicillium, and rarely Cryptococcus, Monilia, Nocardia.

Illustrative Case.—An old Tamil coolie came to the Colombo Clinic in January, 1906, complaining of black urethral discharge dating from several months back. He stated that he had not had sexual contact for several years. The secretion was blackish and contained numerous small granules, which, on microscopic examination, were seen to consist of mycelial articles and spore-like bodies. Various sugar media were inoculated and a fungus was grown, producing a black pigmentation, and very similar also in other characters to *Cladosporium mansoni* (Castellani). In 2 other clinically similar cases, one in a native and the other in a European, a nocardia giving rise to black colonies was found; in another a monilia producing a black pigmentation.

3. **Red Mycotic Urethritis.**—This is a rare condition, but I have seen a few cases in the Tropics and Balkans and south of Europe. I have recently seen a case in New Orleans.

The urethral discharge is usually in exceedingly small amount, mucous or mucopurulent, of reddish or pinkish color. The cases of this condition may be divided into the following groups:

1. The discharge is associated with a red pigment producing cryptococcus or monilia.

2. The discharge is associated with a white monilia fungus plus a red pigment producing cryptococcus or monilia.

3. The discharge is associated with the presence of a white monilia plus a red pigment producing coccus.

4. The discharge is associated with the presence of a white monilia and a red pigment producing bacillus.

Illustrative Cases: Case I.—A little Singhalese boy, six years old, was brought to my clinic in Colombo by his parents because they believed he was passing blood from the urethra. The discharge, examined microscopically, consisted of some leukocytes and numerous budding cells. Several sugar-agar tubes were inoculated and a red-pigment-producing cyptococcus was grown. The child was given an alkaline mixture, and instillations of diluted glycerin of borax were carried out. This, however, did not improve the condition. Urethral injections of a solution of perchlorid of mercury, 1 : 20,000, were then made, and a speedy cure resulted.

Case II.—Mr. L. N., Italian, for the last eight months has noticed a slight urethral discharge which is of a pinkish or reddish color. There is no pain in passing urine. The microscopic examination shows absence of gonococci and presence of very numerous coccal organisms and some yeast-like germs. The fungus (of the genus Monilia) I have grown several times in symbiosis with a red pigment-producing coccus. I have separated the two organisms with some difficulty. The fungus gives rise to cream-like colonies, while the coccus growth is of a beautiful red color.

It is interesting to note that I have found the same coccus together with the fungus in a case in which the discharge has always been white. The discharge becomes red only when the cocci are present in enormous numbers.

Primary and Secondary Mycotic Urethrites.—As is the case with so many other mycoses, the urethral fungal infection may be primary or secondary. I have come across a monilial infection of the urethra in a case of gleet following acute gonorrhea. I

have also seen several cases of urethral moniliasis in diabetic patients in Ceylon; occasionally there was also a heavy external monilia infection forming white membranes which could be easily removed on the glans and corona (thrush of the glans penis, balanitis mycotica, balanoposthitis mycotica).

Mycotic Balanitis, Mycotic Balanoposthitis.—In Ceylon I have come across several cases of mycotic balanitis and balanoposthitis of mycotic origin, generally monilial. The glans and corona are inflamed; there may be a fair amount of exudation, and at times white patches are seen which are easily removed (thrush). The microscopic and cultural examination shows presence of monilia fungi. Diluted glycerin of borax is useful in this condition.

Balanitis Mycotica Mitis.—There is practically no sign of inflammation, the patient merely complaining of slight itching; using cultural methods yeast-like fungi may be found.

Mycotic Vaginates.—I carried out an investigation on this subject in Ceylon during the years 1905 to 1915, and in Great Britain during the last eight years; in Great Britain the work was carried out jointly with Dr. F. E. Taylor; very recently I have done some work on the subject in New Orleans.

It may be said in a general way that in normal women of clean personal habits fungi are not found, or are extremely rare, in the healthy vagina. When vaginal discharge is present fungi are not at all rare. The fungi I have found belong principally to the following genera: Monilia, Saccharomyces, Cryptococcus, Nocardia, Vibriothrix, Oïdium, Aspergillus, Sterigmatocystis, Pencillium, Chladosporium, Alternaria, Hemispora. These seem to be much more frequently met with in hot climates than in cold countries.

Are these fungi, or some of them, really pathogenic? It has been stated that fungi of the saccharomyces type may be beneficent because they have tendency to increase the acidity of the vagina, and this may render more difficult the growth of pyogenic germs.

Probably the fungi I have mentioned when present in small amount act only as saprophytes, but when present in very large

numbers they produce inflammation. I have come across cases of vulvovaginitis in which the mycotic origin was practically certain; like the cases of mycotic urethritis, they may be grouped as follows:

1. With whitish-yellow discharge.
2. With red discharge.
3. With black discharge.

Those of the first group are by far the commonest; the other two groups are exceptional.

Mycotic Vulvovaginitis with White or Whitish-yellow Discharge.—Generally fungi of the genus Monilia in large numbers are found. Three clinical types associated with presence of Monilias may be separated: (*a*) The *membranous type* or "vaginal thrush," white thrush-like patches are present on the mucosa. (*b*) The *purulent type:* no such patches are present, but the secretion is very thick and purulent, and in my experience these cases have not rarely been mistaken for gonorrhea. (*c*) A *mixed type:* thrush-like patches are present and discharge is purulent and thick.

In 1914, in Ceylon, I had the following experience: The surgeon in charge of the Colombo Gynecologic Hospital had a case —a middle-aged Singalese woman—in which a pelvic operation was urgent; a thick, purulent vaginal discharge was, however, noted, and he felt inclined to postpone the operation, as he suspected a possible gonorrheal infection.

I was asked to examine the discharge. No gonococci were present; instead an enormous number of mycelial and conidial elements. Further investigations revealed the fungus to be Monilia pinoyi.

Recently Taylor and myself have found in England several cases of purulent vaginitis of probable mycotic origin. The following species of monilia were found: *Pinoyi*, *metalondinensis*, and *tropicalis*.

Attention might also be directed to the presence of very numerous monilias in certain cases of chronic vaginal pruritus, although the rôle played by monilias in the causation of the pruritus has not been proved. Attention might be called also to a

variety of pruritus vulvæ and pruritus ani, which I described some time ago, caused by the localization of epidermophyton fungi associated with Monilia fungi in the anoperineal region and external surface of the labia majora, without any distinct objective symptoms pointing to an epidermophyton infection (see New Orleans Medical and Surgical Journal, Vol. 79, No. 9, March, 1927).

Mycotic Vaginitis with Red Discharge.—I have seen only one case apparently due to a red pigment-producing cryptococcus present in enormous numbers. It is, of course, possible that the vaginitis may have been of some other origin, and that the cryptococcus present merely caused the peculiar reddish color of the mucopurulent secretion. In addition to the cryptococcus there was present in very small numbers a Gram-negative bacillus which I did not determine, and some very few Gram-positive cocci.

Mycotic Vaginitis With Black Discharge.—In old native women in the Far East occasionally a vaginal discharge may be present in which small black granules are seen. Fungi of the genus Aspergillus and Penicillium have been grown.

Transmission of Fungal Infections by Sexual Contact.—Inasmuch as certain species of fungi have been found in both the male urethra and the vagina, it is not impossible that in certain cases the infection may take place by sexual intercourse.

CLINIC OF DR. J. HOLMES SMITH, JR.

TULANE UNIVERSITY

SICKLE-CELL ANEMIA

WE have here, for presentation, a young colored girl who has been under my care and observation for several months past. This is one of the few cases of its kind recognized in New Orleans, though some authors claim that the condition, or phenomenon, is much more frequent than commonly supposed. The diagnosis in this case is sickle-cell anemia. As a disease, it is of particular interest because of its rarity, and also because of the possibility of confusing it with other conditions. Its importance, as a separate disease entity, is for time to tell. The condition is probably not new, but only during quite recent years does it seem to have been recognized. It is said to be found only in the negro race.

This patient, P. R., a young mulatto girl, now aged fifteen years, first came to the out-patient department of the Charity Hospital during June, 1923, and was admitted to the genito-urinary clinic, because her chief complaint was that the urine was red and stained the clothing. She made a number of visits to the genito-urinary clinic during the next few months, but apparently obtained little, if any, relief.

On December 19, 1923 she was transferred to my clinic with a diagnosis of jaundice. The mother, at this time, claimed that the child's urine was dark and stained her clothing. This urinary disturbance had been occurring, at irregular intervals, since the child was two years of age. Abdominal pains, particularly on the right side, were a prominent symptom at this time, and had been occurring several times weekly over a period of five or six months (the duration of that attack). There was no nausea or vomiting. During some of the attacks there were pains in the muscles and joints. According to the mother, the child's

father had been subject to attacks of "yellow eyes." We have been unable to confirm this statement.

Physical examination showed the patient to be a fairly well-developed colored child, and also well-nourished.

The essential findings were: There was a faint, yellowish tint to the scleræ. The mouth was negative. There was a slight thyroid enlargement. No enlargement of cervical lymphatics was noted. Epitrochlears were palpable, but not very large. Heart: Rate was 82 per minute; occasional extrasystoles were present; there was a faint systolic blow at both apex and base; aortic and pulmonic second sounds were accentuated. Otherwise the heart seemed in good condition. Nothing of note was found in the lungs. The liver and spleen could not be palpated. There was tenderness over the right side of the abdomen, most marked in the lower quadrant and over the gall-bladder area. The colon was spastic. The laboratory reports were as follows: Wassermann reaction was negative. The blood showed: Hemoglobin, 70 per cent.; red blood-cells, 4,675,000; total leukocytes, 15,250, with the differential count as follows—small mononuclears, 38 per cent.; large mononuclears, 9 per cent.; neutrophils, 52 per cent.; eosinophils, 1 per cent. No report was made at this time regarding the morphology of the red cells. Fouchet's test for bile-pigments in the blood was positive. The urine was dark yellow and acid in reaction; specific gravity, 1010; negative for albumin and sugar; there was a faint trace of bile by the iodin test; Ehrlich's aldehyde test showed a strongly positive reaction for urobilin. Radiographic studies of the gastro-intestinal tract revealed no apparent pathology.

A tentative diagnosis of congenital hemolytic icterus was made at this time, because there did not seem to be any obstruction in the biliary apparatus to account for the slight icterus; because of the small amount of bile and large quantity of urobilin in the urine, and, also, because the history indicated that the child's father had been subject to attacks of icterus. The interesting features of the case were not discovered or recognized at this time, probably through ignorance of the condition and mistaking the sickle cells in the blood (it seems reasonable to suppose

they were present at this time) for exaggerated forms of poikilocytes. The patient apparently improved, and was not seen by me again until quite recently.

She next reported at the clinic on October 20, 1926, nearly three years after her first visit. During this interval, she seems to have had but little trouble until shortly before returning to the clinic.

Her complaint, at this time, was that her eyes were yellow, and that there was a painful lump in the right side of her abdomen. No nausea and no vomiting occurred, except when she had the abdominal pain. The bowels were somewhat costive. No history was elicited of any sores on the legs or other parts of the body. Examination, at this time, showed her to be well-developed and nourished. The scleræ had a decided icteric tint, and there was a yellowish discoloration of the soft palate. No definite adenopathies, either cervical or epitrochlear, were distinguished. The tonsils were moderately enlarged. Nothing of note was found in the lungs. The heart showed a slight systolic blow at the apex, and was otherwise negative. The temperature was not taken, but there was nothing at time of examination to indicate that she might have fever. Blood-pressure was low, being 98/55. Examination of the abdomen showed pronounced rigidity of the upper right rectus muscle, with tenderness, upon pressure, below the right costal margin over the gall-bladder region. There was also some tenderness over McBurney's point. There was possibly a slight enlargement of the liver. The spleen could not be felt. No tenderness or tumor masses were elicited over the left side of the abdomen.

At this time the urine was very dark in color, almost a dark mahogany tint. It suggested blood, but did not have the smoky appearance characteristic of bloody urine. The foam test for bile was negative. Iodin test showed a slight trace of bile. Ehrlich's aldehyd test was very strongly positive for urobilin. The urine was otherwise negative.

The blood showed: Hemoglobin, 60 per cent.; red blood-cells, 2,705,000; color index 1 plus; total leukocytes, 6750 (in view of the other findings in this case this count would seem to be too

low); differential count—small mononuclears, 32 per cent.; large mononuclears, 6 per cent.; neutrophils, 59 per cent.; eosinophils, 2 per cent.; basophils, 1 per cent. A study of the stained blood showed marked anisocytosis and poikilocytosis, some red cells of the sickle-cell variety, and a few normoblasts. The Wassermann reaction was negative.

On October 26, 1926, six days after her readmission to the clinic, there was a pronounced improvement in the patient's condition. There was only a slight icteric tint to the scleræ. In fact the color was more of a greenish yellow. (Sydenstricker lays stress upon a greenish hue to the scleræ, though this does not seem to be borne out in every case.) The urine was of normal color, but still contained a large quantity of urobilin. The blood at this time showed: Hemoglobin, 60 per cent.; red blood-cells, 3,742,000; color index, 0.8; total leukocytes, 11,000; the differential count normal. There were still many sickle cells present, apparently as many as at the time of previous examination (between 5 and 10 per cent.). The normoblasts appeared to be increased in number. (According to Sydenstricker, one usually finds an increase in the normoblasts preceding or accompanying a remission.) The fragility test of the red blood-cells showed: Hemolysis began at .50 per cent. saline, and ceased at .20 per cent. saline, showing both an increased fragility and an increased resistance of the red cells. Van den Bergh test: Direct reaction, negative, indirect reaction, 5 units. Gastric analysis showed free hydrochloric acid present in apparently normal amount. The stool was not acholic.

When making the physical examination upon the occasion of her return visit, I must confess to some misgivings as to the correctness of my previous diagnosis of congenital hemolytic icterus. The jaundice, with pronounced pain and muscle rigidity in the upper right quadrant with some tenderness in the lower right quadrant, very strongly suggested the probability of gall-bladder pathology, with possibly a complicating appendicitis. The urine, with its high urobilin content and but a trace of bile, made an obstructive jaundice unlikely, and the van den Bergh test indicated that the condition was, most likely, an hemolytic

one. The blood-picture, however, showing the presence of the characteristic sickle-shaped erythrocytes, made the diagnosis and showed that the condition, while evidently an hemolytic one, was what has now come to be regarded as a separate disease entity. Since the occasion of her return, this girl has been under fairly constant observation until the present time. At times, during this period, there have been occasions when she felt well and complained little, if at all, of either pains or the urinary condition (dark urine which stained her clothing). At other times she has felt weak, has complained of the dark urine, and sometimes has had vague body pains, particularly in the back, but her condition has never been so severe as it was during October. During these periods of distress she is forced to remain away from school. The periods of distress seem to coincide very closely with the dark color of the urine (urobilinuria). When the urine is pale and does not stain her clothing, she generally feels well. When, however, the urine is dark she begins to feel bad, and the severity of the urinary changes seem to regulate or coincide with the severity of her symptoms. Just what rôle the anemia might play as a factor in the production of her symptoms is hard to say. The severity of the anemia and the urobilinuria seem to coincide very closely. The apparent relationship between the degree of urobilinuria and the severity of her symptoms is being stressed because of the undoubted hemolytic nature of this case.

It will be well to observe the various laboratory findings, noted at varying intervals during the period she has been under observation. Before presenting them, however, it is well to state that in addition to a study of stained blood-smears, numerous examinations have been made of moist blood films and the same examined at varying intervals after preparation, sometimes as long afterward as five and six days. In the moist blood-films, after a lapse of twelve to twenty-four hours, sometimes earlier, a large percentage of the red cells (not already sickled) invariably have assumed bizarre shapes, said to be characteristic of the disease. The number of cells undergoing this change was at least 75 per cent. of the total erythrocytes, and this percentage apparently has not varied from month to month.

On November 15, 1926, the blood showed: Red blood-cells, 3,665,000; hemoglobin, 65 per cent.; color index, .9 plus; total leukocytes, 12,250; differential count showed nothing of note. There was slight polychromatophilia, marked anisocytosis and poikilocytosis, some red cells of the sickle-cell variety, occasional normoblast.

December 1, 1926. Blood: Red blood-cells, 2,280,000; hemoglobin, 55 per cent.; color index, 0.1 plus; total leukocytes, 12,500; differential count—small mononuclears, 30 per cent.; large mononuclears, 5 per cent.; neutrophils, 61 per cent.; eosinophils, 4 per cent. There was marked anisocytosis and poikilocytosis. There was about the same percentage of sickle cells. Occasional normoblasts were present and there was slight polychromatophilia.

December 20, 1926, the blood showed: Red blood-cells, 2,055,000; hemoglobin, 35 per cent.; color index, 0.8 plus; total leukocytes, 10,250; small mononuclears, 35 per cent.; large mononuclears, 6 per cent.; neutrophils, 58 per cent.; eosinophils, 1 per cent. Marked anisocytosis and poikilocytosis were present, as were also sickle cells. The urine at this time showed a very strong reaction for urobilin, by Ehrlich's aldehyd test. It is of interest to note that at the time the urine was voided the patient was feeling well, but complained that the urine was beginning to stain her clothing. This was in the morning. By night, she was having back pains, and was forced to remain in bed the following day.

The anemia at this time was very pronounced, indicating that the hemolytic substance, whatever it might be, was particularly active.

January 10, 1927. Blood: Red blood-cells, 2,925,000; hemoglobin, not recorded; total leukocytes, 11,000; small mononuclears, 30 per cent.; large mononuclears, 3 per cent.; neutrophils, 66 per cent.; eosinophils, 1 per cent. There was marked anisocytosis and poikilocytosis, and about the same number of sickle cells. Occasional normoblasts present. Slight polychromatophilia.

January 26, 1927. Fragility test of red blood-cells showed: Initial hemolysis begins at 0.50 per cent. saline; complete hemol-

ysis at less than 0.28 per cent. saline. The results of this test varied but little from that made on October 26th, the increased fragility and increased resistance of the red cells being still present. Van den Bergh test, at this time was—Direct reaction delayed, indirect reaction, 2 units. Urine was dark amber in color and showed a large quantity of urobilin. The blood was stained for reticulated red cells, brilliant cresyl-blue being used for the purpose, but none were found present.

These observations disclose several things: A pronounced anemia with frequent changes in the total erythrocyte count, and in the percentage of hemoglobin, the color index being generally high, sometimes over 1. A total leukocyte count, which, except on one occasion, was constantly above normal limits, varying between 10,250 and 12,500, with little of note in the differential count. Anisocytosis and poikilocytosis were always pronounced, with an apparently almost constant percentage of the red cells showing sickle-cell changes. The percentage of sickle cells seems to have varied but slightly with the exacerbations and remissions of the disease, apparently being between 5 and 10 per cent. of the total erythrocytes in the stained preparations. There were generally some normoblasts, the percentage varying but little. Slight polychromatophilia was always present. With the fragility test, Van den Bergh reaction, and urobilinuria as evidence, there seems little doubt that the patient is suffering from a severe hemolytic process. The patient's general condition seems to be influenced more by the evidences of hemolysis, as indicated by the blood-count and the urobilinuria, than by any change noted in the morphology of the red blood-cells.

But little medication has been given this patient. In fact, so far as we know, there is little we can do other than to use supportive measures. What inaugurates an exacerbation of the disease and what determines improvement, we do not know. We do know that any improvement in this patient's condition is not due to treatment.

DISCUSSION

The sickle-cell phenomenon was, apparently, first recognized by Herrick[1] in 1910. Following this, several cases were reported during the next few years. Emmel,[2] in 1917, very thoroughly described the blood changes found in this condition. During the past five or six years large series of cases have been reported by Sydenstricker,[3] in Georgia, and by Huck,[4] in Baltimore. Recently, Cooley and Lee,[5] in Detroit, have reported finding sickle cells in the blood of 30 negroes out of a total of 400 examined, a percentage of 7.5.

In January, 1926 a case of sickle-cell anemia was reported by Archibald,[6] in the transactions of the Royal Society of Tropical Medicine and Hygiene, occurring in a young Arab boy living in the Sudan. At the time of discovering this case, Archibald was unaware of the existence of this condition in America. Until the report of this case, the disease had only been recognized in American negroes, but it would appear now that the so-called sickle-cell phenomenon, or sickle-cell anemia, not only is widely distributed, but probably occurs wherever there are dark-skinned races. The probability of the Arab boy's having an admixture of negro blood must always be borne in mind. Archibald's report of this case, with photomicrographs of the characteristic blood changes, leaves no room for doubt that his is a case of sickle-cell anemia.

So far, only a limited number of cases have been recognized in New Orleans. The first to be reported was by Jamison, in 1924.

Perhaps, in the majority of instances, the sickle-cell condition is found incidental to examination for other conditions, and may or may not have a bearing upon the condition for which the patient seeks relief. One other case seen by me would illustrate this point.

E. F., colored, female, age twenty-nine, was admitted to ward 40, Charity Hospital, in the service of Dr. J. B. Guthrie, during February, 1925. Her complaint at time of admission was vomiting, and she was not considered to be very ill. Before long, she developed hemorrhages from the stomach, bowel, and uterus,

apparently a purpura hemorrhagica, and died about two weeks after admission. Several days before death, stained blood-smears showed marked anisocytosis and poikilocytosis, and quite a number of the red blood-cells were of the sickle-cell variety. Other blood studies were contemplated, but the patient died before they were carried out. No postmortem examination was secured. What relation the sickling of the red cells may have borne to the condition which caused this patient's death is hard to say. We do not know whether it was but an incidental finding, or whether it was the factor which, being present, determined the fatal outcome.

There are two factors which, until the present at least, would seem to account for not finding the sickle cells with greater frequency. First, unfamiliarity with the condition, and with the appearance of the sickle cells. Second, except during periods of activity, the characteristic changes in the red blood-cells are generally only noted in moist blood-preparations some hours after collection. It is probably well to bear in mind, however, that active cases—patients actually sick with the disease—are not often seen, and are generally discovered accidentally.

So far as known, the condition is confined to the negro race. The Arab boy reported by Archibald may make it necessary to alter our conclusions in this respect, but, on the other hand, the boy was a resident of the Sudan, and he may have had an admixture of negro blood. Or, possibly, all dark-skinned races may be subject to the condition.

It appears to be an hereditary, familial affair, and its occurrence is probably regulated by the Mendelian law governing the dominant factor. As will be set forth later, I have found no evidence of the sickle-cell phenomenon in either the father or mother of our patient, and Archibald claims to have found no evidence of heredity in his Arab boy. The condition seems to occur indiscriminately as to age and sex, and is said sometimes to affect many members of the same family. Graham[7] has summarized the occurrence of the disease very nicely: "It appears to be a familial disease or status, peculiar to the negro race. Chief of its characteristics is an anomaly of the red blood-cells,

evidenced in their tendency to assume elongated sickle or crescent shapes, or various bizarre distortions. In some cases the disease appears to consist in nothing more than this erythrocytic abnormality. Again, certain minor physical disabilities may be added, while in occasional cases there are recurrent paroxysms of acute illness with fever, prostration, pain in the extremities or joints, and evidences of marked hemolytic blood-destruction."

Clinically, it is found in two forms—active and latent. Apparently the majority of cases recognized have been of the latent type, and have been found incidental to examination for other things, or as a result of a check of the families of recognized cases. According to Sydenstricker,[3] the active form of the disease is characterized clinically "by the presence in the circulating blood, or the development in vitro, of poikilocytes of a definite and unmistakable form. Certain symptoms and physical signs are constant, namely, muscle and joint pains, abdominal crises, a peculiar scleral discoloration, general glandular enlargement, anemia, and urobilinuria. The heart generally presents signs common to severe anemia. The liver is generally enlarged. Spleen not felt except in the presence of malaria." A fairly large number of cases either have, or give a history of having had, ulcers on some part of the body, generally the lower extremities.

At this time it may be of interest to quote from Matthes[8] regarding the condition known as congenital hemolytic icterus, a condition, the clinical picture of which our patient resembles, except that she has sickle cells present in the blood, but no reticulated red cells. Matthes says: "Chronic, familial, hemolytic icterus resembles pernicious anemia in many respects, especially during the remittent stage. The severe attacks of pain in the upper abdomen, and the so-called splenic crises are often accompanied by fever. The size of the spleen changes remarkably during the course of the disease, the changes being independent of the severity. At times the spleen may not be demonstrable. The most characteristic feature of the course of the disease is the so-called splenic crisis. . . . Because of the icterus and also the frequent attacks of pain in the right hypochondrium, it is often inter-

preted as gall-stone colic. The blood may show striking increase in the mononuclears and myelocytes, while myeloblasts and nucleated red cells may be present. There is usually a moderate leukocytosis. The icterus is usually moderate and may even be absent. The stool is not acholic. The urine contains urobilin and urobilinogen, but no bilirubin." Reticulated red cells are generally present in large numbers—20 to 30 per cent. of the total erythrocytes. It can readily be seen that our patient has many symptoms and signs common to congenital hemolytic icterus. In the absence of sickling of the red cells, it would be very easy to make a diagnosis of hemolytic icterus—or, if the abdominal pains are severe, to look upon the case as one of gall-bladder disease—and possibly operate.

It must not be assumed that the clinical picture of all active cases will coincide with that of the patient here presented. In fact, there may be a fairly wide range of symptoms complained of, depending upon what particular factor is dominant. It is probable, however, that all active cases, in addition to the sickle-cell phenomenon, will show an anemia, urobilinuria, and other symptoms to greater or lesser extent in accord with Sydenstricker's findings. Should the muscle and joint pains and adenopathies seem to predominate, a diagnosis of syphilis might very readily be made. In fact, it would be considered assured, should the patient happen to have a positive Wassermann reaction. Or, as in the case recently reported by Alden,[9] a leg ulcer might be the outstanding feature, and the patient receive antiluetic treatment. The case reported by Archibald[6] complained of back pain, and was admitted to the hospital with a diagnosis of caries of the vertebra. Again, as set forth under the consideration of this case, the condition might be confused with gall-bladder pathology, congenital hemolytic icterus, or pernicious anemia.

In the so-called latent cases, there is generally nothing in the symptoms or in the stained blood-smear to suggest the presence of sickle-cell anemia. Such cases are generally discovered because of an examination of moist blood-films from many individuals in a search for the condition, or through a

similar examination of blood from relatives of known sickle-cell patients. Such individuals might be observed over long periods of time, and no symptoms referable to the disease discovered. As evidence of this, one individual, to be mentioned later, was under my observation for about one year, with nothing to suggest sickle-cell anemia, and the sickling was found only during an examination to determine the possible incidence of this condition. It is very questionable whether the sickling, in such individuals, has any bearing upon the health of the individual.

As already remarked, the outstanding feature of this disease and the one from which it derives its name, is the peculiar crescentic shape assumed by numbers of the red blood-cells, the percentage seeming to vary with the individual and probably, also, from time to time in the same individual. It is very probable that such cells have been observed in times past, and mistaken for exaggerated forms of poikilocytes. During active periods of the disease, this characteristic change in the red blood-cells is generally easily demonstrable in stained blood-smears, and the sickle cells may vary in number from 5 to 40 per cent. of the total erythrocytes, or possibly higher. During periods of latency, the sickle cells are not generally seen in the stained preparations. When the disease is latent, the diagnosis can only be made by examining moist blood preparations. The procedure for this consists in collecting a drop of blood on a cover slide and then thinning out between the cover slide and an ordinary slide, after which the preparation is rimmed with petrolatum to prevent evaporation. After a lapse of some hours—perhaps from twelve hours on—should the sickling phenomenon be present, numbers of the red blood-cells will begin to assume crescentic and bizarre shapes, said to be characteristic of the disease and not found under any other conditions. The number of red cells undergoing such changes is variable. In some individuals the percentage may be quite low, and, in others, as many as 70 to 90 per cent. of the total erythrocytes may change shape. No cause for this phenomenon has been determined, but it seems to be due to some inherent property of the red cells. Huck[4] carried out some experiments which would seem to prove that

the trouble is inherent in the red cells. After studying the blood of various types of sickle-cell patients by ordinary methods, he tried the following: Normal red blood-cells of the same blood group as the patient's were washed three times in isotonic salt solution, and suspended in the patient's sera of the three types. Fresh preparations were made and sealed. The normal cells in these preparations remained unchanged during a week's observation. Again, red blood-cells from each form of the disease were first washed in isotonic salt solution, and then placed in normal blood-serum from a member of the same blood-group. Fresh preparations were made and sealed. The sickling and bizarre forms appeared in the cells of each type of the disease, in the percentages already determined for that case. Archibald[6] made fresh preparations of normal red blood-cells, previously washed in isotonic salt solution, and mixed with serum from his Arab boy. There was no change in the morphology of the normal cells. Quite recently, there has appeared an article by Josephs,[10] reporting experimental work with blood from sickle-cell patients. These experiments, together with observation by Emmel[2] in 1917, seem to prove that the sickling phenomenon is dependent, first, upon some inherent property in the red cells of sickle-cell patients and, second, upon a substance found in the blood-serum and present in all individuals, both normal and those suffering from sickle-cell anemia.

In his experiments, Josephs obtained the blood by venipuncture directly into a centrifuge tube containing isotonic sodium oxalate. "The blood was then centrifuged at high speed, and the plasma pipetted off. The cells were then suspended in salt solution (unbuffered) and again centrifuged. This was done six times, when it was considered that the cells were completely washed. . . . The salt solutions used for washing were saved separately and numbered. After the final washing, the cell suspension was made up to a volume that it was estimated would contain about 5,000,000 cells per c.mm. The cells were then counted and it was determined that there had been no destruction of the red blood-cells. "As a result of the washings, it was noted that the sickle cells had lost their crescentic shape and

assumed a normal contour. There was no tendency for them to assume the sickle shape, even in coverslip preparations. . . . A few drops of the suspension of washed cells were placed in a small amount of each of the six solutions used for washing, as well as in salt solution and in the plasma from which the cells had been originally taken."

In one case, after standing twenty-four hours, suspensions were examined for sickling. Amongst the cells placed in the first washing there were practically no sickle forms. In those from the second washing, there were about 10 per cent. of sickle forms; in the third, about 30 per cent.; in the fourth, about 10 per cent., and in the fifth and sixth, there were none. In the plasma, there were about 2 per cent. of sickle forms. Similar experiments were successful with the blood from ten sickle-cell cases, and were unsuccessful in 3 sickle-cell cases. No cause was determined for the failures. Washed cells obtained from cases showing sickle-cell changes and, also, cells obtained from patients having no evidence of sickle-cell disease, were placed in solutions used for washing the cells from other patients showing no evidence of this disease. "Sickle cells appeared abundantly, when cells from severe cases were placed in washings from cases in which the blood did not contain sickle cells. . . . From these results, it may be concluded that the substance that becomes attached to the cells, causing them to assume sickle forms, is probably present in all blood, but that only the cells of sickle-cell anemia patients are susceptible to it. . . . There seems to be a substance attached to the red cells, which remains attached in the blood-plasma, but is easily washed off by salt solution."

In this connection, and apparently having a direct bearing upon Josephs's work, Emmel, in 1917, remarked: "There is a substantial and growing body of facts indicating that the mature erythrocyte is surrounded by a membrane consisting, in part at least, of such lipoid substances as lecithin and cholesterol, and that the surface tension associated with membrane of this composition is of such character as to be an important factor in the production of the flattened, biconcave form of the erythrocyte." Emmel believes that the transformation of red cells into sickle

forms takes place in the circulating blood. It is interesting, at this time, to note that cells similar to those found in sickle-cell anemia have been described as normal constituents in the blood of Mexican and Persian deer. (Culliver, quoted by Emmel.)

Huck reports examining fresh preparations of blood from cases of pernicious anemia, secondary anemia, myeloid and lymphoid leukemia, congenital hemolytic icterus, and Banti's disease. There was no change noted in the red cells from any of these conditions after one week. Somewhat similar experiments with moist blood-smears (cultures) were reported by Emmel.[2] This investigator, however, in a case of pernicious anemia, carried his experiments further and with different results. From a patient with sickle-cell anemia, blood was removed aseptically, allowed to clot, centrifuged, and the supernatant fluid removed for experimental purposes. Two experiments were then tried. First: To the patient's serum, normal blood was added. Second: To the patient's serum, blood from a case of pernicious anemia was added. Cultures (apparently moist blood-films) were then made, and kept at room temperature. "In the case of the normal blood, the erythrocytes became softer and more pliable, and showed a tendency to adhere to each other. In the case of the anemic blood, however, the erythrocytes were not only adherent in cords and masses, but quite a number of them eventually presented more or less elongated and crescentic forms with pointed, tapering processes, comparable to those observed in the patient's blood." It would be interesting to observe what changes might occur in red cells from cases of pernicious anemia, if subjected to experimentation such as was carried out by Josephs. The experiments of Emmel and of Josephs would seem to indicate a possible relationship between sickle-cell anemia and pernicious anemia.

In addition to the sickling phenomenon, other changes are generally noted in the blood. The red cells may show microblasts, normoblasts, megaloblasts. There is usually a marked anisocytosis and poikilocytosis, and polychromatophilia is nearly always present. Sydenstricker[3] says that periods of remission are frequently ushered in with a so-called normoblastic crisis.

The sickle cells, at this time, are said to be greatly lessened in amount or to completely disappear, while the normoblasts are very much increased in number. In our patient, there seems to have been little or no change in the number of sickle cells, regardless of her state of well-being, and the normoblasts have never been excessive. The total leukocyte count is almost always definitely above normal, ranging, according to Sydenstricker, between 11,000 and 64,000. There seems to be no change in the differential count.

All seem agreed that during periods of activity there is a definite hemolytic process going on, as evidenced mainly by the large amount of urobilin excreted. This would seem to be confirmed in our case by results of the van den Bergh and fragility tests. Regarding the fragility test in this condition, opinion seems to vary. Sydenstricker found no abnormality in the fragility of the red cells. Cooley and Lee, in their series, report hemolysis beginning as early as 0.45 per cent. saline (one case at least), and terminating, at times, as low as 0.2 per cent. saline. Our patient, on two occasions, had hemolysis begin at 0.50 per cent. saline, indicating a rather marked fragility of the red cells.

The disease, as already mentioned, is said to be hereditary and familial. No sickle-cell changes were noted in the blood of either the father or mother of our patient, in either stained or moist blood preparations. It was noted, however, that in both the father and mother fragility began at 0.50 per cent. saline and both showed a urobilinuria. In this instance it would seem that the patient has inherited a tendency toward an increase in fragility of her red cells.

Pathology.—It is too soon to draw any definite or final conclusions regarding the pathologic findings in sickle-cell anemia. The recognition of the disease is too recent, and the number of pathologic reports too few for any lasting conclusions. Sydenstricker reports three postmortem examinations, one from his own experience and the others from the literature, and he emphasizes certain outstanding features more or less common to all. The heart and liver are generally enlarged; the spleen is

more apt to be small, and in all cases has shown grave lesions in the form of hemorrhages and infarcts. (He believes that this so-called hemorrhagic condition of the spleen may account for the severe epigastric crises.) An emulsion of the spleen from one of the cases showed: Marked hemolytic properties; hyperplasia of the bone-marrow; increased blood destruction.

In contrast to this, we have the findings of Cooley and Lee, who report postmortem examinations upon three individuals whose blood had shown sickle cells prior to death. Regarding their findings, these authors say, "There were no findings noted in any beyond those of the disease causing death, either spleen, liver, or bone-marrow." They also state that they could get no history of leg ulcers, that their patients showed no greenish-yellow discoloration of the scleræ, and that there was nothing to suggest chronic or recurrent anemia. If we are willing to accept Graham's definition of the condition as a "disease or status" characterized by an anomaly of the red blood-cells, which may or may not give rise to symptoms, then these two widely divergent reports might be reconciled. Cooley and Lee apparently had become interested in the sickle-cell phenomenon, and were examining the blood of all negro patients for this condition, regardless of the complaint. Their cases were, no doubt, of the latent type, and had never had any symptoms referable to the sickle-cell condition. The most complete report of a postmortem examination in this condition seems to be that of Graham.[7] Graham's patient died of a streptococcus pneumonia and bacteremia, but he concluded that most of the changes found were of long standing, that they must necessarily have antedated the condition from which the patient apparently died and that, most probably, they were part of the sickle-cell condition. Some of his findings are as follows: "The outstanding lesions are those of the hematopoietic system. The bones show remarkable growth and microscopic changes. The picture is essentially that of a chronic infection or toxic injury to the marrow tissue and medullary bone, with subsequent repair processes and compensatory hyperplasia. . . . In the spleen, the pulp tissue appeared much reduced in amount. The most striking characteristic was the

presence of many sharply outlined rounded areas of brighter red color, that had the appearance of pushing the older parenchymal tissue aside. They were dotted everywhere throughout the organ, and at the periphery gave rise to the nodulations noted on external examination. The general formation, as well as the absence of larger vessels and of well-developed splenic corpuscles, is believed to indicate rather that they are foci of hyperplastic splenic tissue, the so-called splenadenoma. The changes in the liver are those of an active attempt to dispose of unusual amounts of free blood-pigment. In addition, there is evidence that a certain amount of hematopoiesis is taking place. . . . It is to be noted that, if the foregoing interpretation of the splenic nodules is correct, there may be an element of hypersplenism in the pathogenesis of the disease." Again, according to Graham, "The condition here might perhaps better be conceived of merely as a constitutional anomaly, a 'status hemicus,' comparable to the well-known 'status lymphaticus.' As in the latter condition, the state may not be incompatible with good health until such time as the organism may be subjected to special stress of a type capable of bringing to light the inherent weakness."

Prevalence.—Regarding the prevalence of the disease, with particular reference to New Orleans, as already mentioned, cases of sickle-cell anemia have been reported from widely separated localities in the United States, and one case has been reported from the Sudan. In New Orleans there have been about 6 active cases recognized. With the appearance of Sydenstricker's article, some three years ago, I became very much interested in the condition, because of the large number of negroes being seen by me in clinic work. Because of the volume of work and the time necessary to make a survey of many patients, little was done at this time. With the recognition of this case, there was renewed interest in the subject. Numbers of patients presented themselves, who, it was thought, might fit the picture of sickle-cell disease. There was either muscle or joint pains, adenopathies, anemia, or maybe a greenish discoloration of the scleræ. Stained and moist blood-smears were examined from such patients, but without avail. Later, it was decided to make moist blood-smears

from one hundred individuals selected at random, to determine, if possible, the incidence of latent sickle-cell anemia in New Orleans. The result of this was that examinations were made of the blood (moist smears) of 90 colored women and 10 colored men. The red cells from 5 of this number (5 per cent.) showed bizarre forms characteristic of the disease, in percentages varying from 1 to about 70 per cent. Of the positive cases, 3 were women and 2 were men. From this it would seem that the condition is more prevalent in the male, but the number of men examined is not sufficient to draw such conclusions. It has been possible to get in touch with only 2 of these individuals, since the original examination. In neither of these two were sickle cells found in the stained smears. In only 1 of the 5 did the history suggest that his symptoms might be referable to the sickle-cell condition. This patient gave a history of general bodily pains and diseased tonsils. So far, we have been unable to check up on his condition. One of the patients had been under my care for about a year, during which time she had been seen more or less regularly, about twice monthly. She was suffering from an enlarged heart, dilated aorta and vascular hypertension, and her symptoms had been greatly relieved. The sickle-cell changes in her blood were an incidental finding, and do not seem to bear any relation to her condition.

It would seem that about 5 per cent. of the colored population of New Orleans has sickle-cell disease in the latent form, but active cases with symptoms demanding attention continue to be unusual and generally discovered accidentally.

Prognosis.—As one mighr readily infer, the prognosis depends in great measure upon the type of disease present. Latent cases, it would seem, might enjoy a long life and good health without ever experiencing any symptoms referable to the disease. With adults, the prognosis of active cases would seem to be good, some individuals living to old age, but subject from time to time to greater or lesser invalidism from the disease. Sydenstricker claims that the prognosis should be guarded in the case of children belonging to sickle-cell families. Our patient has apparently had the condition from early childhood and, except for the occasional

exacerbations of the disease, she seems to have gotten along very well.

Treatment.—There is nothing specific for this disease. During periods of exacerbation, rest and supportive treatment with iron and arsenic may be helpful. In view of the apparent hemolytic nature of this disease, and, also, the probable close relationship which the spleen bears to it, it is interesting to speculate upon the possible advantages to be derived from splenectomy.

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THE LEUKOCYTES

IT is generally understood that about one-twentieth of the weight of the body is blood, and that in every cubic millimeter of blood in the normal individual there are from 5000 to 10,000 leukocytes. This proportion remains fairly constant throughout life, and variations in this number are characteristic of different types of disease, except where the variation is physiologic.

Since we are unable to study diseased blood-forming organs directly, we must always deduce their condition through the blood-picture, the history, and symptomatology of the case. In making deductions, the physician requires, first of all, an interpretative knowledge of the literature upon blood formation and destruction, and must couple this with direct experience in the blood diseases.

The best success in the modern diagnosis, prognosis, and treatment in the majority of diseases rests upon our information as to the reasons for a certain blood-picture, or in the absence of other subjective symptoms, the reason the blood-picture remains undisturbed.

In the course of routine laboratory examinations a great variety of abnormal blood-pictures are encountered, and not only do the more common irregularities in white-cell percentages appear, but also many unusual and often rare pathologic cells are observed. There are many blood diseases which are not readily recognized, and I am very certain that we frequently overlook interesting blood-pictures, especially those that are subject to sudden change.

Failure of the pathologist to recognize or to properly study such blood-pictures is not always his fault.

Lack of time, inadequate facilities, and improper equipment or insufficient training for such investigation may be responsible. Inability to obtain satisfactory co-operation on the part of the patient and his family, or occasionally failure to secure help from the patient's physician, prevents complete study of a case in some instances.

The blood of a patient may be examined and the patient not seen again for an interval of several days, weeks, or even months, when the entire blood-picture has changed completely.

With the exception of some of the acute surgical conditions and, perhaps, a few of the infectious diseases, the majority of patients should be examined often to obtain the greatest amount of information regarding the blood-picture.

The study of the leukocytes is such an extensive one that, in attempting even a limited review of the literature, one is amazed at the amount of research and investigation that has been carried on, and he is confused over the many conflicting statements and deductions made by the different workers. Particularly is this true as regards the classification, origin, function, and final disposal of the white cells.

The foundation of our knowledge of blood was established by Ehrlich through his introduction of a method of chemical analysis of the cells by means of dyes. Our further knowledge has been greatly advanced through differential studies of the living blood-cells in man and animals by the supravital technic of staining.

Ehrlich divided the white cells into the granular, or leukocytic, forms and the non-granular, or lymphocytic types. Naegeli, Ferrata, Pappenheim, and others use the classification of granulocytes, lymphocytes, and monocytes. To this group, Sabin and Doan[1] add the endothelial phagocyte which they consider different from the other monocytes.

The leukocytes are differentiated from each other by the size, shape, and staining reaction of the nuclei, cytoplasm, and granules in some of them.

The granulocytes are the neutrophils, eosinophils, and basophils. The lymphocytes are the small mononuclear cells, varying in size from that of an erythrocyte to about twice its size.

The monocytes are the so-called endothelial leukocytes of Mallory, or the large mononuclear and transitional types of Ehrlich.

In Sabin's[2] studies on the origin of cells in the blood of the chick embryo, she found that each cell as it first differentiates is specific, *i. e.*, identical monocytes on the third day have a characteristic segregation apparatus and peculiar type of motion; the granulocyte on the third day has its specific type of granulation, chemotactic response, and characteristic arrangement of the granules to the centrosome, and, finally, the small lymphocyte on the fifth day has its peculiar nucleus. Sabin concludes that there are three strains of cells of the connective tissues which contribute to the blood-cells, and that all of these strains give more to the connective tissue than to the blood. The first strain is the angioblasts, which give the endothelium, the erythrocytes, and the monocytes. The second strain is the granulocytes, certain ones of which are phagocytic. They develop specific types of granules, and are specifically sensitive to certain chemicals. Ehrlich thought their functions were related to their specific granules, since the proteolytic action of the neutrophilic leukocyte was thought to occur when the granules were set free from the cell. The neutrophilic leukocyte responds to certain known stimuli, such as the pyogenic bacteria or their toxins; the eosinophilic leukocytes respond to certain others, such as those produced by parasites; and the basophilic or mast-cells are the least understood of the granulocytes. They develop late and remain extravascular. The third strain is the lymphocyte which is widely distributed and, in the chick embryo, the last to develop.

Sabin found the granulocytes in the chick embryo were always extravascular, and she was able to observe the granulocytes pushing their way between endothelial cells and to enter the vessels. The movement, although slow, was a true locomotion. She did not find active ameboid motion of these cells at this stage. In extensive experiments in the rabbit, Muir[3] finds that ameboid movement begins to appear as the nucleus becomes polymorphous. Dickson[4] has seen ameboid movement in myelocytes, and has observed phagocytosis by these cells.

Drinker[5] has seen active phagocytosis by myelocytes which have been washed out of the marrow by a stream of warm physiologic salt solution and kept suspended in oxygenated salt solution. Kite[6] suggests that the phagocytic powers of the living leukocytes might depend to a marked degree upon alterations in surface viscosity which are caused by environmental changes. In making microdissections of leukocytes, he observed that if such a cell is touched with a glass dissecting-needle, and the needle drawn away, a minute thread of hyaline cytoplasm may be seen connecting the point of the needle with the leukocyte. When motile bacteria strike this layer, they stick, and generally do not seem to be able to free themselves. The violent jerking movements made by the bacteria may serve to embed them firmly in the surface of the leukocyte. Not only do the polymorphonuclear leukocytes take up most bacteria, but they apparently digest them very readily. This digestion is accomplished through the medium of proteolytic ferments. All of the varieties of granular leukocytes divide mitotically, but division is practically confined to cells of the myelocytic type. Mitoses in the eosinophils and neutrophils occur up to the stage of the kidney-shaped nucleus. These cells are ameboid and pass readily into the blood-stream by virtue of this activity. If formation is very rapid, they also are driven into the circulating blood by growth pressure.

A leukocytosis, unaccompanied by immediate proliferative activity in the leukocyte-forming bone-marrow, is considered physiologic and occurs in the infant for the first few days of life, the count ranging from 15,000 to 35,000 white cells per c.mm. of blood. This increase is thought to be due to rapid blood formation, and to the influence of feeding. A transient leukocytosis, which is mostly polymorphonuclear, is also seen following digestion, vigorous exercise, after cold baths, and from the effects of certain drugs. In a study of the normal rhythm of white cells, Sabin[7] and others have shown that there is a characteristic rhythm of the total white blood-cells with an interval of approximately an hour's duration, and that the total number of cells is increased in the afternoon regardless of whether food

has been taken or not, and that this entire increase is the result of neutrophilic leukocytes. This may partly explain the so-called digestion leukocytosis. It was found that the neutrophilic leukocytes die out in showers, often of considerable proportions. These dead cells are promptly replaced, though whether from reservoir or directly from bone-marrow they were not certain. They found that the lymphocytes have a shorter rhythm than the leukocytes and that a small proportion of monocytes are normally undergoing division in the circulating blood. They also state that five out of six apparently normal individuals showed a small percentage of myelocytes in the circulating blood. I have frequently seen one or more typical myelocytes in an apparently normal blood, while making differential leukocyte counts.

The pathologic changes which accompany toxic injections and infections may be either a leukopenia or a leukocytosis. Drinker[8] thinks that a transient leukopenia expresses the movement of leukocytes toward areas where they can be of most service. He says that acute leukopenia is never seen in connection with naturally acquired infection, unless the circulation is flooded suddenly with bacteria; that, in the case of bacterial or simpler protein injections, withdrawal of leukocytes from the circulation toward the more important sites of bacterial collection would produce a leukocytosis which would be transient, and would be followed by a leukocytosis as a favorable phenomenon. If, however, the number of leukocytes takes a steady downward course, as is sometimes seen in fatal pneumonias and infections with streptococci and staphylococci, actual leukocyte destruction is in progress, accompanied by advancing aplasia of the marrow. Such a course is of bad import. Certain diseases, of which typhoid is the most notable example, are ordinarily accompanied by a leukopenia throughout their entire course. When typhoid runs a normal course, there seems to be no tendency for leukocytic formation. If infection of another type takes place, such as would occur in intestinal perforation, leukocytosis would be produced very rapidly. In the case of the tubercle bacillus, there is no tendency to leukocytosis, unless meningitis occurs. Leukocytosis seems to have some relation

to the degree to which the infectious processes are localized. There is little tendency for leukocytosis to persist after infection has subsided. It will be maintained as long as the organism successfully combats infection, but will disappear promptly on the removal of the stimulus for its causation.

Practically any foreign substance injected subcutaneously will produce a leukocytosis. The action of such substances, however, depends on the production of local tissue, injury, and the transfer of something from this area to the bone-marrow. Bacteria and their extracts, introduced directly into the blood-stream, produce varying degrees of leukocytosis. Most proteins produce a leukocytosis, the grade of effect depending upon the character and amount of the substance injected, and also on the condition of the leukocytic forming-tissue at the time of injection.

It has been shown that during pregnancy the leukocyte count, the increase of which is polymorphonuclear, may reach from 13,000 to 16,000 per c.mm. This slight increase, which disappears within two weeks after delivery, is thought to be due to the constant existence in the circulation of the mother of small amounts of protein material abnormal for her. It is not known whether this material is derived from the fetal membranes, the fetus, or products of maternal digestion.

There is an invariable increase in the polymorphonuclear leukocyte count within ten minutes following hemorrhage. The height of the leukocytosis is reached in about two hours, and it remains for several days. It occurs whether or not any effort is made to restore blood-volume by infusion. Following a single large hemorrhage, the leukocyte count may remain high for a week.

Farrar[9] made some interesting observations on 150 cases of ectopic gestation, in the Woman's Hospital of New York, with reference to the leukocyte count. She found in these cases that the leukocyte count is a constantly changing figure in the days immediately after operation, and the fluctuation varies according to the amount of fresh blood that is being thrown into the peritoneal cavity, and to the rate of absorption. She says the leukocyte count tends to drop quickly to normal, as the blood in the

peritoneal cavity is absorbed or walled in. Forty-eight per cent. of 150 cases of ectopic gestation had a normal leukocyte count before operation. The leukocyte count was normal in 29 cases of unruptured tubal pregnancy in which there was no free blood, and in 43 cases of ruptured pregnancy in which the blood was walled in. The leukocyte count in these cases was an index to the amount of free blood in the peritoneal cavity, and the polymorphonuclear leukocyte count was increased markedly only in cases having fresh blood in the pelvis, and increased in direct proportion to the amount of recent blood found at the time of operation. Farrar suggests that the leukocyte count must be taken daily, and in critical cases hourly, to be of diagnostic value.

Witter[10] reports findings in a series of 30 cases of postoperative leukocytosis studied every day after operation, to show the general leukocyte curve for a week. She concludes there is a leukocytosis following operation, which reaches its height by the fourth hour after the operation, and returns to normal by the fifth day. The peak varies directly with the duration of the operation and extent of associated trauma produced, other factors being negligible. The leukocytosis was a polynucleosis. The temperature does not rise synchronously with the leukocytes, but reaches its height several hours later.

In a series of 309 cases of appendicitis, Menniger and Hein[11] saw no definite relationship between the postoperative and the preoperative blood-pictures. They support the principles that the total leukocyte count is a measure of body resistance against an inflammatory process up to a certain degree of leukocytosis; that the percentage of polymorphonuclears is an index of the severity of the inflammatory process; and that the greatest aid is to be obtained from a preoperative blood-count as to the indication for operation. They found that the younger the patient, the better is his resistance.

Kilduff,[12] in a paper on the clinical utilization of the leukocyte count, says the presence of persistent leukocytosis is against the benignity of any tumor, and a steadily increasing leukocytosis in malignant disease is a sign of rapid growth or metastasis.

The fate of the leukocyte under normal conditions is un-

known. Their function of phagocytosis is practically carried out in the tissues. We examine them in the circulating blood when they are on their way to functionate, or else they are studied in exudates and sections of lesions in which they are actively at work. It is thought that a certain number of leukocytes are steadily lost by wandering into the lumen of the intestinal tract and many pass out each day upon mucous membranes of the respiratory passages and eventually disintegrate. The high protease content of the leukocyte causes autolysis with great readiness and probably represents the final step in disposal of them.

Eosinophils.—Eosinophilic leukocytes differ from other granulocytes not only from their appearance, but from the reactions in which they take part. It is thought the granules are derived from material outside of the cell containing them, and are not directly a product of the activity of the leukocyte itself. The fact, that they are found only in connection with degenerating tissue of muscle and erythrocytes, supports the contention. As they are found only in connection with tissue containing a relatively large amount of hemoglobin, it is believed that hemoglobin is part of their chemical composition. It is known that eosinophils are more tissue than circulation elements, and only occasionally reach the blood-stream in numbers. Eosinophils increase in the blood-stream in many cases of myelogenous leukemia, in acute bronchial asthma, in skin diseases of a parasitic nature, and in intestinal parasite infections.

In very severe and chronic hookworm infection eosinophils may be absent. This is thought to be due to the disappearance of the cells from the circulation with degeneration of those in the bone-marrow.

I saw a woman, age twenty-four years, four months pregnant, who had been in two different private hospitals for several weeks at a time. She was diagnosed and treated as a case of pernicious anemia. She had a marked secondary anemia, with 15 per cent. hemoglobin. The red cells were slightly above 2,000,000 per cubic millimeter, and there were normoblasts, stippled cells, polychromatophilic cells, anisocytosis, and poikilocytosis. The differential leukocyte count showed no eosinophils.

This patient had the heaviest hookworm infection I have ever seen. The red-cell picture, and the total absence of eosinophils in such a heavy hookworm infection would indicate the possibility of bone-marrow degeneration.

Trichinosis presents the most marked example of eosinophilia, excepting the great increase which might occur in leukemia.

Opie[13] found that, after the administration of Trichina spiralis in the guinea-pig, eosinophils did not occur until the parasites began to pass to the muscles, and the total number increased through some days, as the animal has no reservoir of fully formed eosinophils in the marrow. Eosinophils are ameboid, but rarely act as phagocytes. Opie demonstrated in the guinea-pig that eosinophils move from the bone-marrow to the blood-stream, and from the blood-stream to the sites of bacterial inoculation. I am convinced, that eosinophilia is more constant in infections due to the strongyloid and trichuria than any of the other more common intestinal parasites.

For a period of six years, I examined the blood of a young man who had strongyloid infection, and the eosinophil count was never over 14 per cent. nor under 7 per cent. during the entire time. The parasites were always present.

During the epidemic of 1918, I recall a case of influenza in a child of six years who, on the first examination, had 46 per cent. eosinophils, and who showed a large number of strongyloid embryos. This child has had no treatment, still has the infection, and shows an eosinophilia of about 15 per cent. A young woman college student, whom I have seen recently, has 24 per cent. eosinophils and shows a mild strongyloid infection in every specimen examined. I find the percentage of eosinophils is not by any means an index to the number of parasites present.

Koch[14] has very recently published an article on the study of eosinophils in the vermiform appendix, from which he concludes that eosinophils are normal cellular elements in the appendix from the fifth month of fetal life to old age. He thinks eosinophils normally occur in the mucosa in small numbers, occasionally in the serosa, and rarely in the muscularis, and never within the lymph-follicles in the normal appendix. In acute inflamma-

tory lesions, eosinophils occur in increasing numbers, and then disappear with the advent of suppuration and necrosis. Periappendicitis calls forth a local eosinophilia in the serosa. With obliteration of the lumen, eosinophils disappear from the appendiceal tissues. He believes the eosinophils of normal and pathologic appendices are probably myeloid in origin. Evidence of local proliferation is not obtained in normal or pathologic organs.

Drinker says, in slowly developing lymphocytosis we are almost certain to have a tendency toward eosinophilia. No reason is given for this relation.

Basophils.—The basophilic leukocytes differ also from the neutrophilic leukocytes in the character of their granules. Both mononuclear and polymorphonuclear types are found in the circulating blood, and they contain either fine or coarse granules that take the basic stain.

They are derived from the bone-marrow and from lymph-glands and, like the eosinophils, are, more properly, tissue than blood-cells. They are said to be an evidence of degeneration. The basophils are greatly increased in certain stages of myelogenous leukemia. I have seen several cases of myelogenous leukemia in the early stage, and on examination of the blood found neutrophilic myelocytes only; later, in the same patients, have observed eosinophilic myelocytes, and still later have seen basophilic myelocytes appear. I believe the prognosis, in so far as length of life is concerned, is always unfavorable when basophilic myelocytes are present in numbers.

The Lymphocytes.—The small lymphocytes are slightly ameboid, and the large ones actively so. They are differentiated from the monocytes and granulocytes in not being phagocytic. The cells are derived from lymph adenoid tissue, wherever it is found in the lymph-glands, the spleen, the thymus, and the bone-marrow. At birth, the lymphocyte count is from 50 to 70 per cent. of the circulating white cells. During normal growth of the child this gradually is reduced, and reaches the neighborhood of 20 to 30 per cent. by the fifteenth year, and remains fairly constant in the normal adult blood. During the early years of childhood, the lymphocytes are absolutely increased, and their slow

decrease is an index of normal development. Anything that interferes with the proper growth of the child may arrest the decrease in lymphocytes which should occur and may be signaled by an increase in their number. The lymphocytes are widely distributed throughout normal tissue. They are thought to take different paths to the blood-stream. In the cortical substance of the lymph-nodes there is a dense packing of lymphocytes which are disposed systematically. On the periphery of germ centers, large, actively dividing cells are found. As growth goes on, the adult lymphocytes are forced toward the lymph-sinuses which surround the cortical substance, and are then slowly carried off by the lymph-stream. It is thought few lymphocytes reach the blood-stream by direct movement into the small blood-capillaries traversing the encapsulated lymph-glands, but that lymphocytes readily gain access to the blood-stream in the spleen. Blood moves slowly through the splenic pulp where it has opportunity both to lose and to collect cells. The cells escape from the spleen, probably by virtue of the muscular contractions of the organ. In the bone-marrow, pressure for cell delivery is obtained through growth in an expansile space.

The fate of the lymphocyte is not known. Roentgen-rays and radium have been shown to be destructive to them. Although the lymphocytes are susceptible to dry heat and Roentgen-rays, they are very resistant to toxic agents. Cellular destruction, as is seen in myelogenous leukemia, is not seen in leukemia of the lymphatic type. This is thought to be due to the low proteolytic enzymes in the lymphocytes.

Cottrell[15] reports 12 cases of "infectious monocytosis," a disease of the lymphocytes which he finds is distinct from lymphatic leukemia, the blood-picture being the characteristic feature of the disease, and seen on the first examination of the patient. The total leukocyte count is increased only to a moderate degree, the alteration being mostly in the differential count, showing the lymphocytes to be from 40 to 75 per cent. of all the white cells. He says the salient features of the infectious mononucleosis are: (1) The usual general symptoms of an acute febrile disease of greater or lesser severity; (2) an increase in the

lymphocytes amounting to 40 or more of the total leukocytes; (3) lymphadenopathy; (4) angina—either hyperemia of the fauces and pharynx, or a severe ulcerative and exudative process involving tonsils, uvula, pharyngeal wall, or all three; (5) splenomegaly; (6) presence of the Vincent's organism in the ulcerative and exudative lesions, and (7) increase in the total number of leukocytes. The prognosis is invariably favorable; complications rarely occur. The etiology of the disease is unsettled.

Fox[16] reports observations on the histology of lymphatic tissue, removed during the course of infectious mononucleosis. The lymphatic tissue showed marked hyperplasia. Phagocytosis of fragments but not of whole cells was seen. The lymphocytes appeared soft and degenerating. By supravital staining the cells correspond with the lymphoid elements. No monocytes were seen. He thinks there should be no confusion with any chronic lymphadenopathy at the height of development of mononucleosis.

Bine[17] reports a case of Hodgkin's disease of the skin and mucous membrane with an unusual blood-picture. There were no polymorphonuclear neutrophils. There was 89 per cent. lymphocytes, and 9 per cent. abnormal cells which he thought were myeloblasts. Myeloblasts were not seen in any previous or subsequent examination. He suggests frequent blood examinations, as sudden changes may occur and important blood-pictures be overlooked.

Musser[18] reports 2 fatal cases of leukemia of unusual types, in which the blood-picture in one showed 87 per cent. lymphocytes. He says the lymphocytes could not be classified either into large or small variety, nor was there any granulation in the protoplasm, nor were the cells myelocytes. He thought they were young, immature forms of white cells which might be classified lymphoblasts or myeloblasts. The second case showed only 1 per cent. of polymorphonuclear leukocytes. The other cells were thought to be small lymphocytes. However, the type of cells were not definitely lymphocytes, but rather appeared to be immature cells in which several elements had not had time to fully develop. He says that in no sense is leukemia a clear-

cut disease entity which always runs the same course, as is the usually accepted conception of the disease, that bizarre and abnormal manifestations of the disease takes place, and these deviations from the normal tend to confuse the etiology of the disorder. He suggests that leukemic reactions occur in a certain number of cases with, or in association with, septic processes within the body.

I examined the blood of two sisters, ages fourteen and sixteen years, who were thought to have had influenza. They were treated by their father, a druggist. One girl was taken sick three or four days earlier than her sister. Both gave histories of fever, sore throat, loss of appetite, and extreme weakness which lasted for several days. Their convalescence was slow, and after the fever subsided they gained strength very slowly and were very anemic. After three or four weeks' time a physician was consulted, and he requested a blood examination. Both girls showed a red-cell picture simulating very closely a primary anemia inasmuch as there were all forms of pathologic red cells, a low count, and a rather high color-index. The younger girl showed a leukocytosis, with a predominance of cells that I thought were large lymphocytes. The older girl showed a leukocytosis with 11 per cent. neutrophilic myelocytes. Some of the other cells I was unable to classify. The patients were not seen again for about three weeks, at which time the white blood-picture had become practically normal, and the red-cell picture in each was greatly improved. Earlier and more frequent examinations of the blood in these 2 cases would have been instructive.

The Monocytes.—In addition to the granular leukocytes, there are numbers of other large phagocytic cells which were formerly spoken of as large mononuclear and transitional cells, but in most of the recent literature are known as the monocytes.

The monocytes have been described as proliferating from capillary endothelium and moving out into the surrounding tissue. In addition to the cells arising in this way, certain of them apparently arise from supporting reticulum of such tissues as the marrow, spleen, and lymph-glands. They reach the blood-

stream constantly, and in small numbers. These cells phagocytize carbon and particulate matter.

Mercklen and Wolf[19] state, that both clinical and pathologic observations indicate that changes in the monocyte count of the blood depend on changes in the reticulo-endothelial tissue. Monocytes may be of reticular or endothelial origin. The monocytes of typhoid are caused by hyperplasia of the reticular tissue, spleen, glands, Peyer's patches, etc. The same is true of the monocytes of smallpox, chickenpox, mumps, measles, and whooping-cough. The acute diseases that are accompanied by a monocytosis are those that induce immunity. In endothelial monocytosis, there is a tendency to hemorrhage and purpura. Examples of such conditions are seen in infectious endocarditis, at the end of septicemia, and in typhus. Among chronic diseases, monocytosis is found in malaria, leishmaniasis, kala-azar, relapsing fever, and amebic dysentery. It is an indicator of the response of the reticulo-endothelial system to parasites. Decrease in the number of monocytes is noted in certain pernicious anemias and in highly acute infections. They prevail in certain types of leukemia. Such a monocytic leukemia lasts for years, though always fatal. Persistent monocytosis may co-exist with myeloid and lymphatic leukemia. It is believed that Hodgkin's disease is the one condition in which there is a slight but constant increase of these cells.

Cunningham, Sabin, Sugiyana, and Kindwall[20] have studied the rule of the monocyte in tuberculosis in rabbits, and advance the theory that the tubercle bacillus attacks one strain of cells, namely, the monocyte. They think that the effect of tuberculosis on the whole system of the monocytes consists primarily in a marked overproduction of the diffusely scattered reticular cells, which are the parent cells of the monocytes, and which are also the parent cells of all the other white blood-cells. They believe the tubercle bacilli are alive in the cells, and that the bacilli live and multiply within the cell, and that, although the monocytes phagocytize the tubercle bacilli and then fail to destroy them, it would seem particularly important to seek for methods of decreasing the phagocytic activity of these cells, or else of in-

creasing their cytoplasmic activities so that the ingested bacilli will be destroyed instead of being allowed to live and multiply. They suggest that it is of major importance to discover the chemical substances which cause the change of monocytes into epitheloid cells, thinking that the discovery of such a substance is the first step toward producing an antibody for them. They believe, with a substance by which the overproduction of monocytes might be checked, the problem of immunity in tuberculosis might be more analogous to the problem in those diseases which have already been controlled.

In following the blood of rabbits which have been infected with massive doses of tubercle bacilli, they found a marked correlation between the progress of the infection in the tissues and the condition of the blood. First, there was an actual and marked increase in the percentage of the monocytes which would go as high as 53 per cent., and, second, the normal ratio of monocytes to lymphocytes is reversed. An acute tuberculosis in the rabbit showed the monocytes of the circulating blood far in excess of the lymphocytes when the lymphocytes were markedly and constantly higher than the monocytes. Even though the actual numbers of the monocytes were somewhat above normal, they found arrested tuberculosis without exception. They were able to correctly judge the condition of the animal by following the ratio between these two types of cells.

Goldzieher and Peck,[21] in a series of experiments, studied the rôle of the reticulo-endothelial system in the defense of the organism against infectious agents and their toxins. Thirty mice were vitally dyed by subcutaneous injections of trypan blue, and 25 were left unstained. Pneumococci Types 1, 2, and 3 were passed through several animals so that their virulence was raised. A saline suspension of fresh twenty-four-hour cultures of all of these were made. The animals were divided into four groups. Groups 1 and 3 each contained 10 vitally dyed animals, while Groups 2 and 4 contained equal numbers of unstained animals. Each of the animals in Groups 1 and 2 received intraperitoneal injections of 0.5 c.c. of the saline suspension containing viable organisms, while those in Groups 3 and 4 received

equal amounts of heated (60° C. for one hour) suspension. The animals were then killed one, two, six, and twenty-four hours after inoculation and the liver and spleen examined. They found the early response of the reticulo-endothelial system in experimental animals very striking. The first demonstrable changes were those of proliferation. which set in shortly after infection and gradually increased with the progress of the infection. Degenerative changes became apparent somewhat later, and also more marked with the duration of the process. The reticulo-endothelial system responded more quickly to the administration of bacterial toxins than to bacterial infection. The final response, however, was greater in the latter. In vitally stained animals, the recticulo-endothelial cells at first responded somewhat more slowly, but finally the increase in response exceeded that of the unstained animals—both those in which there was active infection, and those in which toxins alone were administered. During the course of vital staining a number of animals died, and the livers were found to be greatly infected with parasites. The animals which survived were free from infection. The authors think death resulted because vital staining interfered with the mechanism of resistance of the animals.

The immediate response of the reticulo-endothelial system to infection was by proliferation, as, in human cases, the increase in the size of the spleen was due mainly to proliferative changes. The reaction of the reticulo-endothelium of the mouse was more striking in the liver than in the spleen.

Shortly after these experiments with bacteria and their toxins, Goldzieher and Peck[22] attempted to determine whether injections of various drugs, such as mercuric chlorid and sulpharsphenamin, might not induce an analogous process. They again used mice in the experiment, some vitally stained and others left unstained. They found that injections of mercuric chlorid and sulpharsphenamin had a striking effect on the reticulo-endothelial cells which was equally apparent in both cytoplasm and nucleus.

The reticulo-endothelial cells of the liver and spleen showed response to mercuric chlorid or sulpharsphenamin with marked

swelling and vacuoli formation. They suggest that the stimulation of the reticulo-endothelial activities either by mercuric chlorid or sulpharsphenamin may possibly yield antibodies, which circulate in the blood and body fluids, and eventually may reach the spirochetes. The usual antisyphilitic medication destroys spirochetes mainly by means of reticulo-endothelial stimulation. It is suggested, that the therapeutic effect of mercuric chlorid and sulpharsphenamin are based upon stimulation of reticulo-endothelial function.

In the July Archives of Pathology, Jaffe[23] gives a general review of the reticulo-endothelial system. He says the following functions have been attributed to the reticulo-endothelial cells in connection with infections: (1) The phagocytosis and intracellular destruction of the micro-organisms; (2) the reception, detoxication, and digestion of the waste products that are formed during the process of inflammation, including the toxic substances liberated from the bacteria; (3) the absorption of soluble toxins; (4) the secretion of the antibodies (bacteriolysins, agglutinins, antitoxins, and other bodies). Jaffe considers the monocyte problem still far from settled. He believes that the normal monocyte is derived from the reticulo-endothelium of the spleen, liver, bone-marrow, and lymph-glands, and doubts if much is gained by subdividing the large mononuclear cells of the blood. He also suggests that differences between single cells may be due to their different ages and states of functional activity.

In a recent study of desquamated endothelial cells in the blood of normal and tuberculous rabbits, and with normal human blood, Sabin and Doan[24] conclude that there are four strains of white cells in the normal circulating human and rabbit blood: Granulocytes, lymphocytes, monocytes, and endothelial phagocytes. In their review of the literature, they found that the theory that endothelium gives rise to free phagocytic mononuclear cells was first advanced by Mallory, in 1898, in connection with the study of the lesions of typhoid fever in which he found desquamated endothelial cells in clots of the heart's blood. The first observations, according to Sabin and Doan, of the finding of

cells in the peripheral blood were by Rowley, in 1907, who found cells, similar to those described by Mallory, in the blood of a patient with tertian malaria, and in 3 cases of lymphatic leukemia. All the patients showed endothelial phagocytic cells, which contained both red and white corpuscles. They also quote a number of other investigators who have observed similar cells in a variety of conditions—cholera, ulcerative endocarditis, leukemia, chlorosis, staphylococcus infection, typhoid fever, cancer, purpura, and many other diseases. In these experiments Sabin and Doan have shown that desquamated endothelium is a practically constant constituent of normal blood, that it is not identical with the monocytes, and that its numbers are increased under many pathologic conditions. They think that there are two strains of phagocytic mononuclear cells in normal blood—desquamated endothelium and monocytes.

They describe the cells as appearing in normal blood in a great variety of forms and sizes. Stained with Wright's blood-stain, the chromatin of these cells is massive and made of closely packed granules. Some of the nuclei have definite nucleoli and they interpret the clear zones as interspaces. The cytoplasm is so fragile that some of the cells appear as nuclei with thin, torn veils of cytoplasm around them. The cytoplasm of the long, the small, and the intermediate types is faintly basophilic, and is entirely clear and structureless, except for certain refractile bodies. From their observations, they think that some of the endothelial cells in the blood are degenerating, while others are alive and performing the function of ingesting and digesting débris. In a series of 20 rabbits they found the endothelial cell counts varying from 0.5 to 8 per cent. In normal human blood, they were present up to 4 per cent. in 80 per cent. of the counts. In tuberculous rabbits, there was a fairly constant increase up to 17 per cent.

Peterson,[25] in some experimental work, concludes that the endothelial phagocytes are different from the monocytes, and are rare in normal human blood.

In an investigation of the normal and pathologic fragmentation of red cells and the phagocytosis of these fragments by

desquamated endothelial cells of the blood-stream, Doan and Sabin[26] have shown that the fate of the fragments is taken up by the wandering endothelial phagocytes.

They use the three terms, "clasmatocyte," "wandering endothelial phagocyte," and "macrophage" as synonymous and distinct from monocyte. They found clasmatocytes with fragments of red cells in the circulating blood, in the plasma, and in the connective tissues, and they were able to differentiate them when studied with the supravital technic from eosinophilic leukocytes, with which they have been confused in the literature. They found that the clasmatocytes or endothelial phagocytes not only take in and destroy whole red cells, but they also dispose of the results of the fragmentation which is constantly going on in the blood-stream. With any increase in fragmentation, there is an increase in the number of clasmatocytes containing these fragments. They think that it is this strain of cells, perhaps, which carries the major part of the work of breaking down and conserving hemoglobin, whether by phagocytosis of whole red cells or of their fragments. Their final conclusions are that there is constantly some breaking down of red cells in the circulation by fragmentation; that the fragments of red cells, as well as whole red cells, are phagocytized and destroyed by clasmatocytes; that, when there is an increase in fragmentation in abnormal or pathologic states, desquamated cells of the blood-stream, as well as the clasmatocytes of the tissues, increase proportionately and take in these fragments, and that these cells can be distinguished from eosinophilic leukocytes by the nature of their granules, by the type of motility of the cells, and by a negative peroxidase test. They found that desquamated endothelial cells, clasmatocytes, in the circulating blood are positive to the peroxidase test only when they have taken in positive material.

In many instances I have seen cells, resembling the endothelial phagocytes described by Sabin and Soan and others, which, on account of the uncertainty of the classification, I have either failed to enumerate or have classed with the mononuclear leukocytes.

SUMMARY

1. On account of the sudden changes that may occur in the blood-picture in diseased conditions, the best information regarding the leukocytes is obtained by frequent examinations.

2. A better understanding of the function of the leukocytes, and of the influences which stimulate their production and distribution, will result in a greater success in the diagnosis, prognosis, and treatment of many different diseases.

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THE VALUE OF THE OBSTETRIC HISTORY IN MAKING A DIAGNOSIS OF SYPHILIS

THE important part played by syphilis in causing stillbirths is well recognized. Most of the studies on the subject have been from obstetric clinics[1, 3, 4, 5, 8, 9, 10, 11] on women during their child-bearing period, and have involved a study of the tissues of the dead fetus and of the placenta. The diagnostician is often faced with the problem of interpreting the history of a stillbirth in his patient, when the patient's own story, which involves no report of a pathologist, is his only source of information concerning the event. The present study is an effort to determine how much importance may be attached to a mere history of a stillbirth. The term "stillbirth," as used in this article, has a somewhat different meaning from that given in obstetric nomenclature. The following requirements must be met in the history: Delivery of a dead fetus after the fourth month of gestation was spontaneous, and not unduly long; was not preceded by an illness sufficiently severe to confine the patient to bed; there was no swelling of the face, eyelids, or hands.

This study is based upon 388 consecutive cases, seen by the writer in one of the medical Out-patient Clinics of Charity Hospital for negro females above the age of thirteen years. The series included only 2 pregnant patients. The very large number of patients visiting the Out-patient Department of Charity Hospital are sorted, so that only those whose chief complaints are constitutional are sent to the various medical clinics. Naturally, a rather large number of those sent to the colored women's medical clinic belong in the gynecologic clinics, and are transferred after being studied in the medical clinic. Cases of this

sort are included in the present study. Although visits to the Charity clinics cost the patients nothing, the colored rarely seek the services of a physician except when diseased.

The negro women of this group make a particularly suitable group for studying the value of the obstetric history for diagnostic purposes, since 70 per cent. of the entire group and 83 per cent. of those with syphilis had been pregnant, averaging three times each. The group of 388 is distributed according to age by decades as follows: Second, 16 per cent.; third, 36 per cent.; fourth, 25 per cent.; fifth, 11 per cent.; sixth, 7 per cent.; seventh and above, 4 per cent. The incidence of syphilis was greatest in the fourth decade, being present in nearly one-half of the patients of that age group. Next, in the order named, were the fifth, third, and second. Above the age of fifty the disease occurred much less frequently.

In order to determine of how much value a history of one or more stillbirths might be in the diagnosis of syphilis, the subject was approached in two ways: First, all patients in the group of 388 who gave a history of one or more stillbirths were studied for the frequency of syphilis. Second, all undoubted cases of syphilis were studied as a group for the frequency of a history of stillbirths.

Of the 388 patients studied, 64, or 11 per cent., gave a history of having had stillbirths. Only 11 of the whole group, or 17 per cent. of just the stillbirths, showed neither clinical nor serologic evidence of syphilis. Of the 64 cases, the Wassermann reaction was positive in 21, 33 per cent.; negative in 34, 53 per cent., and in 9 cases it was either not done, or was anticomplementary or unsatisfactory. If these 9 cases and 2 treated cases with negative reaction are omitted, the Wassermann positive cases amount to 40 per cent., and the Wassermann negative cases to 60 per cent. Among the cases with negative Wassermann reactions were 15 cases, and among those with questionable reactions 3 cases (a total of 18) with clear-cut evidence of tertiary syphilis. There were 11 cases of cardiovascular syphilis, mainly aortitis, with or without aortic insufficiency or aneurysm; 3 cases of stricture of the rectum; 2 cases of neurosyphilis; one each of periostitis and

destruction of soft palate. Therefore, in 39 cases the Wassermann was either positive or there was clear-cut evidence of tertiary syphilis. If the 6 remaining cases with questionable Wassermann reactions and 2 cases, previously treated, with negative reactions be omitted from the total group of 64, the group of 39 in which a positive diagnosis of syphilis can be made represents 70 per cent. Among the remaining cases in which a proved diagnosis of syphilis cannot be made are 14, or 22 per cent. of the 64, who gave symptoms strongly suggestive of active syphilis. These were made up of the following groups: Seven presented cardiac symptoms, mainly precordial pain and nocturnal "smothering"—a feeling as if inadequately supplied with air, which usually makes the patients sit up in bed—but they do not describe deeper or more rapid breathing. Neither of these symptoms in this group of 7 was considered severe or typical enough to make a certain diagnosis of heart disease. Their hearts or aortas were not dilated, as shown by roentgenograms or physical examination. Three complained of pain in superficial bones, with localized tenderness, worse at night, but clear to roentgenographic examination; 2 were relieved immediately by antiluetic treatment; the third did not return. Two were suspected of neurosyphilis, but neither the symptoms, nor reflex changes were sufficiently definite to make a clinical diagnosis. The spinal fluid was not studied. One case showed a general glandular enlargement, the glands being small and firm and not tender. Another complained of weakness of a few months' duration, and had a moderate secondary anemia, otherwise unexplained. The two stillbirths in this case had occurred eight or ten years before. In most of these 14 cases, the symptoms referred to were probably caused by syphilis, but one cannot be sure.

To summarize, in 64 cases who had had at least one stillbirth, 21 had a positive Wassermann reaction, and among those with negative or questionable reactions there were 18 other cases with definite tertiary syphilis, clinically, making 39 in which the diagnosis was reasonably certain. In addition, the diagnosis was strongly suspected clinically in 14 other cases,

which, when combined with the two preceding groups, makes a percentage of 83. Eleven cases (17 per cent.) showed no evidence, other than the obstetric history, that they might have syphilis.

In order to study the frequency of stillbirths in known cases of syphilis, only latent and tertiary types may be considered, since those in the primary and secondary stages of the disease have not had an opportunity, except rarely, to bear a stillborn fetus due to their disease.

There were 42 cases of clinical, tertiary syphilis in patients who had had one or more pregnancies. Twenty-three were cardiovascular cases, meeting at least one of the following requirements: (1) Widened aortic shadow in a person less than forty-five years old, as shown on the teleoroentgenogram and measured for the hemicircle, according to the technic of Granger.[12] Four cm. was considered the highest normal width in persons who had passed the age of forty-five; (2) physical signs of aortic insufficiency with other definite evidence of syphilis; (3) unquestioned aneurysm of thoracic or abdominal aorta, subclavian or innominate arteries. Unless there was roentgenographic evidence of erosion of the spinal column, the diagnosis of abdominal aneurysm was made only when two other observers agreed upon the clinical diagnosis. (There was only one case of abdominal aneurysm in the series.) Aneurysms in the chest were always studied by the teleoroentgenogram, or by fluoroscopy, or by both. All the cases in this group had definite symptoms of cardiac failure.

Six cases showed bone involvement, proved by roentgenographic examination. Three cases had combined cardiovascular and bone syphilis. There were 4 cases of neurosyphilis, clear cut as to history and physical findings, but without spinal fluid studies; one had a positive blood Wassermann; another had been treated with arsphenamin several years before, and had a negative reaction, as had the third.

Five patients had evidence of rectal syphilis. Two had proctitis, without stricture, with ulceration and nodule formation over the mucosa, and one of them had a positive Wassermann reaction. Wassermann test was not made on the other. Both

were studied carefully for amebic and bacillary dysentery, with negative findings. Three others had typical, low, band-like, rectal strictures with little or no ulceration. One showed multiple nodules over the rectal mucosa. Two were thirty-two and thirty-three years old, respectively, with short histories of bowel disorder. The other was thirty-nine years old and gave a history of alternating diarrhea and constipation for seven years. Of these 3, 1 had a positive Wassermann reaction, 1 a negative reaction, and for the third it was not recorded.

The 3 other cases of the group were as follows: One case of multiple skin gummata with positive Wassermann reaction; and one with destruction of the soft palate and evidence of aortitis; the last showed a typical scar of a leg ulcer which had recently healed under arsphenamin treatment. The Wassermann was negative in the last 2 cases.

These cases were analyzed for the incidence of stillbirths, for Wassermann reaction, and for the agreement of the two. There was a positive history for stillbirths in 24 cases (57 per cent.), and a positive Wassermann in 19 cases (45 per cent.). If 3 cases, with negative Wassermann tests, who had received considerable antiluetic treatment be omitted from the entire group, the Wassermann positive cases make 49 per cent. Of the 24 cases with stillbirths, 6 were Wassermann positive, 15 negative, and 3 questionable. Of the 19 cases with positive Wassermann reactions, 6 gave a history of stillbirths. Five cases were negative for both obstetric history and serology. In 3 cases, all the pregnancies ended in early miscarriages. These cases had no more opportunity of having stillbirths than did the sterile patients. If they are omitted from the entire group, the percentage giving a history of stillbirths becomes 62, as compared with 49 per cent. with positive Wassermann reactions. The group of 42 was also analyzed for the number of pregnancies each patient had had. Of those who had had stillbirths, 63 per cent. had been pregnant more than three times, while only 35 per cent. of those without a history of stillbirths had been pregnant four times or more.

There were 54 patients whose Wassermann reactions were positive, in whom no clinical evidence of active syphilis could be found, or the evidence was not more than strongly suggestive. These were considered as having either latent, or questionably latent stages of the disease. Of these, 7 had never been pregnant, and in 6 all the pregnancies had ended in early miscarriages. Excluding these, the group consisted of 41 patients. Fourteen, or 34 per cent., had had one or more stillbirths.

There was, then, a total of 83 patients who had been pregnant one or more times, in whom the diagnosis of tertiary, latent, or questionably latent syphilis was definite. Of these, 38, or 46 per cent., had had stillbirths.

DISCUSSION

The history requirements, already enumerated, were designed with the purpose of eliminating, as far as history could, causes of stillbirths other than syphilis.

According to the statistics presented by Williams,[11] if dystocia, prematurity, and toxemia can be eliminated, the probability that a stillbirth is due to a cause other than syphilis is very small. Since premature infants usually live for a few minutes, at least, dystocia causes long labors or operative deliveries, and toxemia gives rather striking symptoms preceding delivery, it seems rather likely that the history as required would indicate what stillbirths might be syphilitic. A history of the fetus being macerated points most strongly to syphilis as the cause of fetal death.[1, 9] It has been difficult to get satisfactory information on that point in this series of patients, and it has, therefore, not been included as data in the present study.

Pregnancy may be looked upon as a test for syphilis comparable to the Wassermann reaction. It is probably true, that if Wassermann reactions were done often enough throughout the course of the disease, every case of syphilis would at some time give a positive test. Likewise, should a woman with syphilis become pregnant during certain stages of her disease, the pregnancy would almost surely end with the birth of a dead, syphilitic fetus, usually after four months of gestation. There are probably

other stages of the disease in the mother when the pregnancy would result in a full-term, syphilitic, but living baby, and still another later stage, even in the untreated, when a healthy child might be born. Then, a stillbirth may be considered as a positive result of the "pregnancy test" for syphilis, as a living, healthy baby is a negative test. Whether this test is positive or negative in an untreated, syphilitic woman depends upon the stage of the disease. Treatment of the mother may prevent syphilis in the fetus, though inadequate to cure the mother. How to interpret negative "pregnancy tests" is often as puzzling as the negative Wassermann. It would seem that the chances of getting a positive test in a syphilitic woman run somewhat in proportion to the number of times the "test" is performed, as shown in the group with tertiary syphilis. It is, of course, of the greatest importance to know the period of years in which the patient's healthy children were born. A number of women studied in this series evidently gave, between the ages of seventeen and twenty-five years, birth to several healthy children. Then, at the age of thirty-five, they had syphilitic aortitis or other tertiary manifestations, yet gave no history of stillbirths. This was due to the fact that during the ten years preceding the development of tertiary manifestations they had been sterile—usually on account of salpingitis. Since no such cases as these have been excluded from the series, it is astonishing that such a high percentage of patients with syphilis should give a history of stillbirths. In evaluating this study, much depends upon the accuracy of diagnosis of the cases of tertiary syphilis with negative Wassermann reactions. In most of these cases the writer has had the benefit of the opinions of either Dr. Chaillé Jamison, chief of the clinic in which this work was done, or Dr. Birney Guthrie, into whose wards some of the patients were admitted.

It is interesting to speculate upon an explanation as to why there were 11 patients of the 64 who had had one or more stillbirths, who gave no clinical or serologic evidence of syphilis. Were these "false positives"? Were they stillbirths due to causes other than syphilis not revealed by history or physical examina-

tion? It is, of course, impossible to know from the data available. Chronic valvular heart disease of rheumatic origin has been given as a cause of stillbirths. That is a condition usually not difficult to diagnose from the history or physical examination. It has not been given a prominent place in this study, due to its rarity among this group. Four cases of mitral stenosis (without evidence of aortic involvement) were found in the 388 cases studied. One of those with a clear history of rheumatic fever had had a stillbirth, but, since she had a positive Wassermann reaction and other evidence of syphilis and had never suffered from heart-failure, she was not excluded from the series. Browne[1] denies that stillbirths from women with negative Wassermann reactions are caused by syphilis, because he was unable to find *Treponema pallida* in tissues of such fetuses. He does not state, however, that he was able to find them in all fetuses from women with positive Wassermanns. In the light of Moore's[7] studies, it is rather likely that most of these 11 cases represent instances of marked latency of a syphilitic infection, and are entitled to antisyphilitic treatment.

It was hoped, when this study was begun, that it might give some light upon Moore's[7] interpretation of Colles's law. His evidence indicates that when a woman without clinical or serologic evidence of syphilis bears a syphilitic child, she is not, herself, free of the disease, but is an example of a peculiar form of latency, for the production of which the pregnancy is partially responsible. Hutchinson[2] had suggested in 1878 that pregnancy modified the usual course of the infection. The writer had hoped to contrast syphilis in the patients who had not been pregnant with those who had had pregnancies, but the former group was so small that it could hardly be used in comparison with the latter. The group of 43 patients with outspoken tertiary manifestations contained only 1 nullipara, which indicates that the protection offered by pregnancies is in many cases either not very lasting or powerful. Among these were 17 who had had five or more pregnancies each. Several of these showed the most widespread and advanced syphilitic processes. As examples: One patient who had had five pregnancies showed aortitis, and

advanced involvement of many bones; another with nine pregnancies had an extremely dilated ascending aorta, and aneurysm of the innominate artery; a third, who, though only thirty-three years old, had had fourteen pregnancies, ten of which were stillbirths, showed a stricture of the rectum; the patient with multiple skin gummata had been pregnant six times, and had had two stillbirths. In some of these cases, many years had elapsed after the end of their child-bearing period before tertiary symptoms developed, but for several, as for the third case above, this was not true. McDonough[6] suggested that the protection lasts only during the child-bearing period. Records on all these cases were not complete enough to analyze them accurately for the time relationship of child-bearing period to development of tertiary manifestations.

SUMMARY

1. Requirements are outlined for a simple history designed to indicate which prematurely ended pregnancies might have been due to syphilis. These are called stillbirths.

2. Of 388 colored women studied in an out-patient clinic, 64 gave a history of stillbirths which suggested a syphilitic cause.

3. Of the 64 patients, 61 per cent. were definitely syphilitic; 22 per cent. probably syphilitic; 17 per cent. were without clinical or serologic evidence of the disease.

4. Of 42 patients with clear-cut clinical tertiary syphilis, 57 per cent. gave a history of stillbirths, and 45 per cent. had positive Wassermann reactions. Patients who had had stillbirths had been pregnant a greater number of times than those who had not.

5. Of 41 patients with latent or questionably latent syphilis, 34 per cent. had had stillbirths.

6. The value of pregnancy as a test for syphilis is discussed.

7. The theory of the protective influence of pregnancy against tertiary syphilis is discussed.

CONCLUSION

The history of a stillbirth which meets certain requirements is of great value in diagnosticating syphilis in women.

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THE RESULTS OF ONE COURSE OF TREATMENT WITH OIL OF CHENOPODIUM ON A GROUP OF PATIENTS HEAVILY INFESTED WITH INTESTINAL PARASITIC WORMS

IT is the custom of the clinical laboratory of the Department of Medicine to examine the stools of some of the orphan asylums at least once a year. This examination is made in the clinical laboratory by the junior medical students, each specimen being checked by an instructor.

The stools are examined especially for intestinal parasites—ova, larvæ, and amebæ—and also for blood, pus, monilia, fat, and food remains.

This year, after the first examination, the children were treated and then re-examined three months later. I thought that it might be of interest to you to know the results of these examinations before and after treatment.

Total number examined	227
One or more infections	180
No ova or larvæ found in	47
One type of infection found in	86
Two types of infection found in	55
Three types of infection found in	29
Five types of infection found in	1
Trichuris trichiura	136
Ascaris lumbricoides	56
Hymenolepis nana	34
Strongyloides stercoralis	24
Oxyuris vermicularis	11
Uncinaria americana	3
Endameba coli	52
Endameba dysenteriæ	2

Treatment.—Boys between the ages of eight and ten years were given 0.6 c.c. of oil of chenopodium, and those between the ages of ten and twelve were given 1 c.c. The evening before treatment was begun the boys were each given 30 c.c. of a saturated solution of Epsom salts, and the next morning, at 10 o'clock, 0.3 c.c. of the oil were given to each one, the smaller children being given the oil by floating it on ice water, while the larger ones were given the oil in capsules. At 2 P. M. the same day the second dose of oil was given, and the larger boys were given 2 capsules, or 0.6 c.c., and the smaller ones were given 0.3 c.c. At 6 o'clock the same evening they were all given 30 c.c. of saturated solution of Epsom salts.

In their "Manual of Tropical Medicine" Castellani and Chalmers[1] report that the International Health Board of the Rockefeller Foundation, in 1917, stated that the results would not support the statement that this oil was the most effective remedy for the treatment of ankylostomiasis and, further, that it produced at times alarming symptoms and even death.

"It is either used alone or with oil of eucalyptus in the proportion of three parts of chenopodium to one part of eucalyptus. The method of administration is to forbid all solid food after midday, to give a purge of Epsom salts at 4 P. M., and then, at 6 P. M., the first dose of sugar containing chenopodium. This is continued at two-hour intervals until the full dose has been taken. Two hours after the last dose 1 ounce of Epsom salts is taken by an adult and repeated, if necessary, in another two hours.

"The dosage of oil of chenopodium is as follows:

	Minims for three doses.
1– 2 years of age	2
3– 5 years of age	3– 5
6–10 years of age	6– 9
11–16 years of age	10–13
17–50 years of age	14–16
Over 50 years of age	12–14

It can be given on sugar or in gelatin capsules

"Epsom salts, 5 pounds to 5 gallons of water.

4 drams to child from	1– 5 years
8 drams to child from	6–10 years
12 drams to child from	11–15 years
16 drams to child from	16–20 years
24 drams	above 20 years

"No alcohol or acids are to be ingested for a period of twelve hours before and after treatment. Pregnant women should not be treated in this way.

"Treatment should be repeated after ten days if necessary, as determined by the microscopic findings."

Results of Treatment.—The following cases, positive before treatment, were found to be negative after treatment:

Endameba coli	5
Ascaris lumbricoides	4
Trichuris trichiura	7
Oxyuris vermicularis	3
Trichuris and Hymenolepis nana	4
Hymenolepis nana	1
Trichuris trichiura and strongyloides	1
Trichuris trichiura, Oxyuris vermicularis, and Endameba coli	2
Trichuris trichiura and Ascaris lumbricoides	2
Trichuris trichiura, Ascaris lumbricoides, and Endameba coli	2
Trichuris trichiura and Endameba coli	1
Trichuris trichiura, Hymenolepis nana, and Endameba coli	1
Trichuris trichiura, Ascaris lumbricoides, and Endameba coli	1
	34

Comments.—Chenopodium is a neurotoxin. An overdose may produce vomiting, dizziness, deafness, tingling of the hands and feet, albuminuria, muscular incoördination or semicoma. These symptoms may be prevented by free postvermicidal purgation. If toxic symptoms occur, they should be met by stimulation and external heat.

We were careful to produce free purgation before the oil was given, in order to remove as many parasites as possible, mechanically, and to prevent a possible intestinal obstruction in the cases heavily infested with ascaris.

In some of the cases the infection may have ended spontaneously within a period of three months; and, again, others which were negative after treatment became reinfested.

If three such treatments had been administered at ten-day intervals, we believe that the results would have been quite satisfactory.

Conclusion.—We believe that the oil of chenopodium is the best general vermifuge. It is comparatively safe. No child suffered any ill effects, and it may be seen from the results of this small amount of treatment how effective the full course would be in the different types of intestinal parasites.

In this heavily infested group of children it is interesting to note that one course of treatment with oil of chenopodium was effective to the extent of eradicating worms from twenty-nine out of one hundred and eighty patients, giving an efficiency rate of nearly 17 per cent. as judged by the completely cured cases.

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SYPHILIS AND THE SLIDE TEST

It is generally agreed that a serologic test for the diagnosis of syphilis, to confirm clinical observations, is much needed. This is true, because this infection imitates the clinical manifestations of practically every other disease. It is present in cases presenting themselves for treatment with other conditions, not at all, or only remotely, due to syphilis, but at the same time masking that disease. Such cases can be handled more satisfactorily if syphilis is known to be present, and the disease also treated.

There are other patients, in whom syphilis was never suspected until a serologic test calls our attention to it. Repeated tests, both precipitation and complement fixation, subsequently confirm the original finding. I do not believe that a case should be diagnosed syphilitic on one laboratory test without a positive history or some clinical reason. Neither do I overlook the fact that syphilis is present, with a negative serologic test, when clinical findings suggest the disease. If we diagnose syphilis where it does not exist, we subject a patient to a long course of unnecessary treatment, and, besides, he may develop a psychosis. On the other hand, if we fail to recognize a positive case, the disease goes on unhindered, so that the results of an error in diagnosis may have far-reaching consequences, and materially effect the welfare of the patient.

Occasionally, one method of testing the blood for syphilis is negative and another is positive, due perhaps to a different antibody to which the test is sensitive. So I like to use both the complement fixation and the precipitation test on each patient's blood, especially on the ones in which there is likely to be some doubt.

A simple slide test has been developed and used in the laboratories of clinical medicine for over a year. It is a combination of three separate and distinct tests for syphilitic serum—the gel, the flocculation, and the turbidity tests. Thousands of bloods

have been checked with both Wassermann and the slide test, and with the clinical findings. I have found in my own hands that, when a definite characteristic precipitate forms, the Wassermann will also be positive and in the majority of cases there are other evidences of the disease.

Technic of Antigen Preparation.—Fresh veal hearts are selected, and the superficial fat removed. The muscle is ground in a sausage grinder, and spread on paper and dried by an electric fan. After it is completely dried, it is reground and extracted with ether. Four hundred c.c. of ether are used to each 100 gm. of powdered heart and allowed to act for ten minutes, shaking frequently. The ether is filtered off, and 300 c.c. are again added to the heart and treated in the same manner. The heart-muscle is again treated with 300 c.c. of ether, and again a fourth time, the ether in each instance being filtered and discarded. The heart-muscle is now dried free from ether, and, for each gram of muscle, 5 c.c. of 95 per cent. alcohol are added, and maceration is allowed to continue for three days at room temperature. (Same proportion as used in the preparation of the Kahn antigen.[1]) The extract is filtered off, and made up to the original volume with 95 per cent. alcohol. This constitutes the defatted alcohol heart-extract for the antigen. Six dg. of cholesterol and 3 c.c. of glacial acetic acid are added for each 100 c.c. of the alcoholic extract. This is filtered after solution is effected, and constitutes the finished special antigen for this test.

The test is easy to perform and is recommended because of its simplicity. Heating of the serum is unnecessary and no special laboratory equipment is required. The precipitate forms in large clumps and is easily seen. The materials needed are:

1. Two drops of clear serum from the patient.
2. A clean test-tube or a 4 c.c. vial for mixing antigen and distilled water.
3. The lower one-half of a 1 c.c. pipet with a Wright's rubber bulb.
4. An ordinary glass slide.
5. A 1 c.c. or capillary pipet for placing the serum on the slide.

6. A toothpick for stirring.

Two minutes' time is allowed for the reaction to take place, after stirring well on the slide for twenty seconds with the toothpick.

Technic of Collecting Blood.—Draw 1 (or more) c.c. of blood with a dry, chemically clean, glass syringe. Defibrinate by stirring with a wood applicator or allow sufficient time for the clot and serum to separate. Centrifuge to obtain perfectly clear serum. Or the blood may be taken from the finger or ear in a capillary pipet as is done for the Widal test. A capillary pipet is cut off squarely with a file, leaving a half inch of the capillary portion. The blood from a good stick is welled up in drops; the puncture is wiped dry with a towel after each drop or two, so that the blood will form drops and not run over the surface. These are touched to the pipet, and about an inch of the large portion of this is filled with blood by capillary attraction. A small strip of adhesive plaster, $\frac{3}{4}$ inch long and $\frac{1}{4}$ inch wide, is passed over the capillary end of the pipet, sealing it. After clotting (about five minutes) the top of the clot is broken away from the sides of the pipet with a toothpick or wood applicator and the capillary tube dropped into a test-tube. It is centrifuged in this tube for about two minutes at one-half speed (full speed of centrifuge 1500 revolutions per minute), or until the serum separates above the clot. Two drops are taken up with a capillary pipet and placed near the middle of the slide. Blood may be collected in a Purdy tube, and defibrinated or allowed to clot, and centrifuged. This tube has a small diameter at the bottom, and a small amount of blood will form a relatively narrow column so that the serum can be easily pipetted off.

Technic of Antigen Mixture.—Cut a 1 c.c. (graduated 1–10) pipet in half and attach a Wright's rubber bulb, thus making a graduated medicine dropper. Wash out pipet with 95 per cent. alcohol before going into stock antigen. Take up 0.2 c.c. of antigen, and place in a dry test-tube. With the same pipet take up 0.4 c.c. of distilled water. Run this into the antigen, and mix thoroughly by alternately sucking up and forcing out the mixture with the pipet, holding the tip of it against the bottom of the tube. The colloidal suspension should be opalescent and remain

good for one hour. It should not precipitate on a slide if rocked alone.

Technic of Test.—With a capillary pipet, cut to where the outside diameter is 2 mm. (size of the lead in an ordinary pencil), take up the serum and drop two full drops on the center of a scrupulously clean microscopic slide. With the pipet in the antigen mixture, place 3 full drops alongside, but not into the serum. With a clean toothpick mix serum and antigen and continue stirring the mixture for twenty seconds (by watch or count). The spread of fluid should be limited to an area the size of a twenty-five-cent piece. Tilt the slide gently from side to side for a two-minute period, and read the reaction.

Reading.—By indirect light (sunlight, electric light, or even daylight from a window, looking toward the light with a black surface beneath the slide for a background), four general readings can be made:

1. Strongly positive—shown by heavy, flocculent, white precipitate.
2. Positive—definite white precipitate.
3. Weakly positive (doubtful).
4. Negative—no precipitate or no change from its first appearance.

Interpretation.—Definite to strong, positive reactions usually conform to the intensity of the Wassermann reaction. Weak positive reactions should be disregarded for diagnostic purposes. In general, the test is not as delicate as a properly performed Wassermann.

Comments.—The reactions should not be made in the presence of fevers over 101° F., in moribund conditions, or upon old hemolyzed or contaminated blood-specimens. The antigen colloidal mixture is more sensitive after it has stood about five minutes than if used immediately. An occasional blood will give a strong reaction if tested five minutes later. Prepare the antigen-distilled water mixture first, so that it can stand while the serum is being separated. The life of the complete antigen is about three months. After that time it may become unstable. When this occurs it precipitates with the addition of any blood-serum.

It is granular and cannot be recognized from moderately positive bloods.

The antigen can be reconditioned by adding more glacial acetic acid. Add enough acid to make the remaining antigen 0.5 of 1 per cent. (10 c.c. of antigen and 0.05 c.c. of acid). This increases the life of the antigen much more than before.

The *p*H is near 2.8 when first prepared, but the acidity gradually decreases so that at the end of three or four months it is not sufficient. If the *p*H is maintained constant by adding enough acid from time to time, the antigen would remain active indefinitely, but this procedure can only be carried out in a laboratory. More acid cannot be added when the antigen is first acidulated, because it would not be sensitive enough. The range of acidity for best results is between 2 and 3 per cent. If the acidity is too low, the antigen is unstable and if too high, it is not sensitive enough.

The heart extract should be obtained from fresh veal hearts, and should be perfectly dry before extraction. If the alcoholic extract is allowed to stand at room temperature or in an ice-box for two or three months before the antigen is completed, a much better product is obtained.

This test becomes negative earlier in treated cases than does a delicate Wassermann reaction. Therefore, in such cases it is not as sensitive as the Wassermann.

Conclusion.—The slide test, which has given us so much valuable information, is recommended because of its simplicity together with its high degree of specificity for Wassermann positive bloods. It was designed especially for the physician who wishes to test the serum reaction of his patient for his own information rather than for the laboratory where the more elaborate and complicated blood-serum tests can be properly performed.

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CLINIC OF DR. RUSSELL C. PIGFORD

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THE RELATIONSHIP OF CRYPTORCHIDISM TO ENDOCRINOLOGY

EXPERIMENTAL and clinical evidence is rapidly accumulating in support of the theory that each of the glands of internal secretion has its specific effect on the human economy. The chief obstacle to an earlier and a more exact understanding is the probability that one gland is capable, to a certain extent, of either protagonizing or antagonizing the effect of another, and that, in the hypofunction or absence of one structure, there is a vicarious function of another. Such a picture of disturbed physiology is not infrequently the problem of the internist.

It is, therefore, always worth while to take every opportunity that presents itself for the discussion of these matters. It is with this viewpoint in mind that I wish to present an example of an endocrinopathy, and discuss it from various angles, and emphasize the evidence presented of the interrelation of the various, important endocrine glands and their secretory disturbances.

CASE RECORD

The patient, a white male, twenty-two years of age, has lived on a farm all his life, until a few months ago, when he came to the city to take employment as an usher in a theater. He was admitted to the surgical service of Dr. Urban Maes, Charity Hospital, about two months ago, complaining of severe, right iliac pain. An examination at that time revealed an undescended right testicle, with a small, indirect hernia on the same side. He was operated upon by Dr. I. M. Gage, and the right testicle was brought down into the scrotum. Since the operation he has had no return of the pain, although he feels, at times, an aching

sensation in the region of the right external ring. Dr. Gage informs me that at operation the vas was found to be very small, with a poor blood-supply, and difficulty was experienced in bringing the testis down. Dr. Gage is rather dubious of the prospects.

While the boy was in the hospital an additional diagnosis of Fröhlich's syndrome was made. An uneventful recovery from the operation followed. He was discharged from the hospital, and referred to the Out-patient Department, Dr. John H. Musser's service, for further observation and treatment. The following additional information was recorded:

The **family history** is irrelevant, but interestingly negative. His father, aged fifty, and his mother, aged forty-eight, are both in good health. He has four brothers, ages sixteen to twenty, and four sisters, ages seven to thirteen, all of whom are normal in every way, none presenting any conspicuous evidence of endocrine disturbance. The father is of medium frame, weighing about 160 pounds, but is from a family of large-framed individuals. The mother is of a medium height, and weighs about 140 pounds. She comes from small-framed stock. The brothers and sisters are all large for their ages, but otherwise apparently normal. The family history is negative for constitutional diseases.

The **past history** is incomplete. The patient had an injury in the right parietal region in early infancy, when he fell from the bed to the floor. At the age of eight years he fell over a bench, striking the occiput on the floor, at which time he was rendered semiconscious for about an hour. This accident was followed by severe pains in the head for several days. He had measles at the age of fourteen years, and at nineteen he had pertussis.

His **present illness,** further elaborated, yielded much important information. He does not recall the exact date of the onset of his present trouble. It has been very insidious. The condition dates back at least as far as his grammar-school days, when he first had "achy" temporal headaches, which at times radiated to the occiput, and were more often present only on the right side, but, when on the left, they were definitely more severe.

These headaches have gradually become more frequent, and for the past six years they have recurred daily. They seem to be more severe in the summer than in the winter. For the past six years, the boy has had attacks of non-projectile vomiting accompanying the headaches, but apparently without direct relation to them. The vomiting, which frequently occurs several times a day, he attributes to a "weak stomach."

For the past eight or ten years he has had "growing pains" located in the right iliac region. Six years ago, while in swimming, he had an acute attack of severe, right iliac pain, accompanied by vomiting. This pain gradually disappeared after a week, but since that time he has always noticed, when lifting, a feeling as though something were slipping in that region. He has had several recurrences of the acute attack. Weakness, dizziness, vomiting, headaches, and cold perspiration have accompanied the pains. Fever has been a variant.

System Review.—*Eyes:* The patient has never worn glasses, and so, far as he knows, his vision is good. Wheel-like images are experienced with the severe headaches. *Ears:* Occasional tinnitus aurium is present. *Nose:* The olfactory sense is lost except for strong odors. He complains of an obstruction in the nose. *Mouth:* There has been no disturbance of the taste for sweets, acids, salts, and bitters. Ptyalism is an annoyance, and, at intervals, he has herpes labialis with a cracked tongue. He has had recurrent tonsillitis with a dryness of the throat. His voice has not changed. It is still high-pitched. His *cardio-respiratory* system has given him no symptoms. *Gastro-intestinal:* His appetite is quite variable. Excessive hunger and thirst have been absent. Occasional eructation of greasy foods is experienced. The bowel activity varies greatly, from several, soft to watery, very offensive stools in twenty-four hours to a hard, spastic stool every ten days. Tarry stools have been noted at times. *Genito-urinary:* There has never been any polyuria. He urinates a moderate quantity two or three times a day and once at night. His genito-urinary history is otherwise negative. The only symptom referable to the *osseous system* is a stiffness of all joints, experienced after the patient has been at rest for a

short while. He says that when he attempts to rise he has difficulty in getting on his feet, and feels "like an old man." *Growth:* His growth was rapid until six years ago. This seems to be a family trait, as the same is true of all his brothers and sisters. Since the age of sixteen he has increased very little in height. The size of his shoe, $7\frac{1}{2}$ to 8, and his hat, size 7, have not varied in this time. His weight at sixteen was 130 pounds; immediately

Fig. 190.—Showing the general contour of the body. The broad hips and somewhat elongated, slender, feminine upper extremities are the outstanding features.

before coming to the hospital it was 144. His weight fluctuates. He loses 8 to 10 pounds rapidly, and just as rapidly regains it. *Mental:* His mind has always been active. He finished high school, advancing with each class, and failing only in geometry. He did not worry over his work, and was never forced to labor with his studies. He likes hunting and fishing, and his companions are youths of about his age. He reads moderately of rural life, and is not interested in novels or "love stories." He

neither cares for, nor does he shun the opposite sex. Libido has not appeared. He sleeps soundly, and rarely dreams.

Physical Examination.—This reveals many interesting abnormalities. The temperature is 98.6° F., with a pulse rate of 80, and respiration 18. The blood-pressure is 104/80. The patient is well oriented, attentive, co-operative, and answers questions deliberately and accurately. He possesses a fair amount of intelligence, and, although no specific tests have been made to determine his mental age, I would estimate it at about sixteen

Fig. 191.—The broad face, high skull (superciliary line to the top of the skull), soft, beardless skin of the face, and slender, tapering fingers are seen in this view.

years. The general appearance of the face is that of a youth of about sixteen years of age, but is smooth and covered with lanugo hair. It is rounded, the length and breadth being equal. It is without character and expression. The frontal region is prominent. The bony landmarks, such as the superciliary ridges, the nasal bone, and the mandible, do not stand out in the general physiognomy. The zygomata are rather conspicuous.

The *skin* of the body is thin, warm, dry, and inelastic, being supported everywhere by a thick panniculus adiposis. Over the

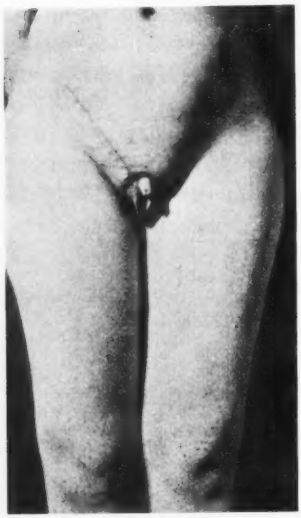

Fig. 192.—Well-developed scrotum with infantile penis. The right testicle can be seen immediately below the external ring. The fold around the penis cannot be considered a feminine characteristic because of the well-developed scrotum.

Fig. 193.—Roentgenogram of the skull showing the small sella turcica.

face and neck it is of a pinkish hue, is smooth and studded with freckles. The patient says that he freckles very easily when in the sun. Over the trunk and lower extremities it is milk white and, when seen with a shaded light, is marked by very small pittings. The pitting is especially marked over the lower abdomen. The mucous membranes are slightly pale.

The *scalp* is covered by a thick crop of rather coarse, reddish-brown hair of normal distribution. The rest of the body is covered

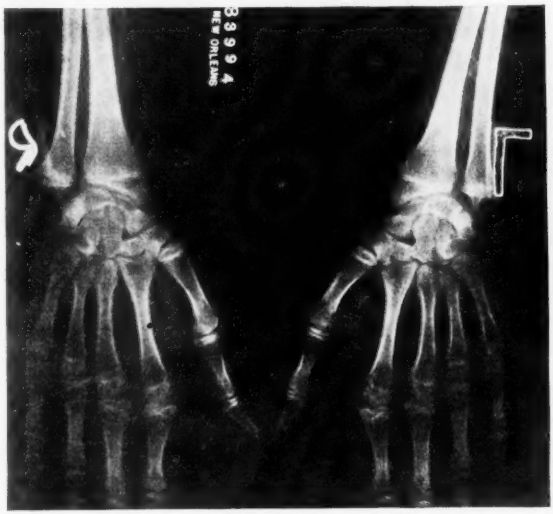

Fig. 194.—Plate of forearms and hands. The epiphyseal cartilages in the ulna and radius should be ossified before the twentieth year of life.

by a scanty amount of lanugo. There is no beard, and the pubic and axillary regions are free from hair. The eyebrows are silky and show no thinning.

The *fat distribution* is quite characteristic. It is moderately increased over the anterior chest and markedly increased over the lower abdomen, hips, and the upper part of the thighs. There is no increased fat over the dorsum of the hands and feet. The muscles are not well defined. They are made flabby and obscure by the general superfluous adipose tissue of the body.

The *frame* is of medium height. There are no osseous deformities. A waddling gait is suggested.

RESULTS OF ANTHROPOMETRIC STUDIES

Height, 168 cm. Weight, 62.7 kg.
Torso, 81 " Lower stride, 87 cm. Span, 169 cm.

Head:
Interparietal, 14 cm. Intertemporal, 12.5 cm. Bizygomatic, 13.5 cm.
Fronto-occipital, 19.5 " Face length, 12.5 " Skull length, 12.5 "
Jaw (horizontal ramus), 11 cm.

Chest:
Ant. post. diam. (nipple), 19.5 cm. Circumference (nipple), 82 cm.
Lateral diam. (nipple), 25 "

Abdomen:
Ant. post. diam. (umbilicus), 17 cm. Circumference (umbilicus), 80 cm.
Lateral diam. (umbilicus), 25 " Circumference (ant. iliac spine), 91 cm.

Extremities:
Intertrochanteric diam., 36 cm.
Intertrochanteric circ., 100 "

Arm length, 28 cm. Circumference { upper ⅓, 28 cm. / middle ⅓, 26.5 " / lower ⅓, 26.5 "

Forearm length, 26 cm. Circumference { upper ⅓, 25 cm. / middle ⅓, 20 " / wrist, 17 "

Hand length, 19.75 cm. Width (thenar), 10 cm., (knuckles), 8.75 cm.
Finger length, 10.75 cm.

Thigh length, 36.5 cm. Circumference { upper 57 cm. / middle, 51 " / lower, 43.5 "

Leg length, 40 cm. Circumference { upper, 35.75 cm. / middle, 36 " / ankle, 25.5 "

Foot length, 27.5 cm. Width, 10.5 cm.

Attention is directed to a few of the more important measurements. It will be seen that the span is greater than the total height of the body. The upper body length is less than the lower stride. The horizontal ramus of the jaw is somewhat shorter than would be anticipated in an individual of this age and osseous proportions. The ratio of the bizygomatic diameter to the face length is suggestive of infantile proportions, as the face at this age should be longer than the width. Again, the face length

is the same as the skull length. In the infant the face length is much less than the skull length, and as the individual reaches the adult proportions the face length approaches and exceeds that of the skull. The intertrochanteric measurement of 36 cm. demonstrates that the large hips are not due entirely to the adiposity in this region, but in part to an actual widening of the bony pelvis. The osseous measurements of the extremities show no gross abnormalities. However, in taking the circumferential measurements some interesting figures are observed. It will be seen that the lower abdominal circumference is greater by 11 cm. than the upper. The circumference of the arm is practically the same throughout, varying only 1.5 cm., and tapering from above downward. The intertrochanteric circumference, while showing a large hip-measurement, is deceptive, because of the extra deposit of fat that hangs immediately distal to the level of the measurement.

The *reflexes* are not abnormal. The pupils respond to light and accommodation. The knee-jerks are hyperactive. The cremasteric reflexes on both sides are intact.

The *glandular system* shows no conspicuous abnormality. There is neither general nor local adenopathy.

Head.—The eyes are negative. Fundus examination is negative, and the visual fields, as determined by Dr. George L. Hardin, show no temporal narrowing. An error of refraction has not yet been corrected. The ears are normal. The size of the nose is in proportion to that of the face. The bridge is fairly well developed. The lips are somewhat thickened and slightly protruding. The teeth are poorly kept, and have an appearance of immaturity. The tongue is pale and coated. The papillæ are small. The tonsils are hypertrophied and scarred. Dr. Homer Dupuy reports chronic follicular tonsillitis and left ethmoiditis. The patient is to be operated upon at a later date, while the sinus is being treated locally.

The *voice* is weak and high-pitched. The *thyroid cartilage* does not protrude. On palpation, the thyroid gland is of normal size, and is without irregularities. The isthmus can be felt.

Chest.—The breasts are rather prominent. The chest is sym-

metrical. Expansion is 6.5 cm. The percussion note is universally hyperresonant. There is no evidence of a persistent thymus. The breath sounds are vesicular. *Heart.*—No abnormalities can be detected in the heart. The rate is 80, the rhythm regular. The sounds are normal in character.

Abdomen.—Above the umbilicus the abdomen is somewhat flattened; below, it is rounded and protruding. The protrusion below is produced by a thick layer of fat in the region. The abdominal wall is hypotonic, with a poorly developed musculature. The lower abdomen, laterally, padded by a thick layer of fat, curves gracefully out over the wide ilia below, giving the appearance of female hips. Posteriorly, there is an extra thick pad of fat over the lower lumbar region. There is a long inguinal scar, the result of the recent operation, on the right side. The liver, spleen, and kidneys are not palpable. Tenderness is elicited over the scar in the region of the external ring. The abdomen is otherwise negative.

The *anus* and *rectum* present no abnormalities.

Genitalia.—The penis is well formed, but very small, being about 2.5 cm. in length. There is a suggestion of a fold at the root of the penis, but this is probably due to the adiposity in this area. The scrotum is small, wrinkled and baggy. The left testis lies in the extreme upper scrotal cavity, is about 1 cm. in diameter, and is hard and tender. The right testis is not in the scrotal sac proper, but can be brought down with some difficulty. It is about 2.5 cm. in diameter, is firm, and slightly tender. Palpation reveals a doubtful epididymis.

Extremities.—The arms are long, rounded, and with graceful lines, again suggesting feminine features. The hands are somewhat shortened, with slender, tapering fingers. The nails are long, narrow, and thin. There are no transverse ridges. There is a fine passive tremor of the fingers, which the patient says is quite annoying at times. The wide hips cause the thighs to swing inward, giving one, at first glance, an impression of genu valgum. The musculature here, as elsewhere, is not defined. The legs are without normal contour, being large in the lower third. Flat feet are present, making the feet appear wider than normal.

Laboratory Examinations

Urine:

Specific gravity,	1.020
Reaction,	acid
Albumin,	negative
Sugar,	negative
Acetone,	negative
Indican,	negative
Bile,	negative
Microscopic,	negative

Blood picture:

Hemoglobin, 78 per cent. (Dare)
Erythrocytes, 4,875,000
Color-index, 0.8
Leukocytes, 9250

Small mononuclears,	23
Large mononuclears,	6
Neutrophils,	62
Eosinophils,	8
Basophils,	1

No abnormalities of the red cells noted in the smear. No malaria plasmodia found.

Sugar tolerance test (100 gm. dextrose by mouth):

Blood:
Fasting, 95 mg. per 100 c.c.
2 hours, 110 mg. per 100 c.c.
3 hours, 95 mg. per 100 c.c.

Urine: No glucose was present in the urine during or after the test.

Stool: Offensive, soft, dark brown, containing large particles of undigested food. Unchanged starch in moderate quantities. Fatty acids present. Occult blood test is negative. No ova, parasites, or cysts were found.

Basal metabolism: (—) 22 per cent.

Blood Wassermann: Negative.

Roentgenograms: The sella turcica is very small. Views of the wrists, including the hands, show no union between the diaphyses and the epiphyses, and as this usually takes place between the ages of eighteen and twenty, there is delayed union in this patient. Plates of the teeth are negative.

SUMMARY

The essentials in the anamnesis are: (1) A history of two head injuries during infancy and childhood; (2) insidious onset of such symptoms as temporal headache, vertigo, tinnitus aurium, obstipation, asthenia, stiffness of joints, and a moderate fluctuation of weight. Such a chain of symptoms would immediately direct attention to a pituitary disturbance. In addition, the cryptorchidism, together with the attacks of pain in the region of the undescended testicle, the arrest of psychic and mental development, with absence of the libido, would point to infantilism of testicular origin. In the physical examination and laboratory studies, the outstanding findings, to aid in the diagnosis of hypopituitarism, are the characteristic distribution of the adipose tissue, the failure of development of the flat bones,

particularly those of the face, the vascular asthenia, the small sella turcia, and the increased sugar tolerance. Such findings as the under-developed testes, persistence of the lanugo hair without beard, axillary or pubic hair, the skeletal disproportions and the failure of ossification of the epiphyseal cartilages, are in accord with the picture of gonadal insufficiency. From such data, the conclusion may be reached that we are here dealing with a pluriglandular endocrinopathy involving chiefly the gonads and the pituitary gland.

DISCUSSION

Head trauma during infancy or childhood is a not infrequent cause of dyspituitarism. The pituitary gland situated in the sella turcica at the base of the skull is well protected from extraneous forces. However, as a result of severe trauma, causing basal fractures, it might well be the seat of permanent derangement. The loss of the olfactory sense lends support to the theory of head trauma as a possible causative factor in the production of the dyspituitarism in our patient.

In some animals, for example the fowl, the normal position of the testes is in the abdominal cavity. In others, they are extra-abdominal. The blood-supply of the testes and ovaries in the human, springing from the aorta just below the origin of the renal artery, immediately groups the gonads as abdominal organs. The migration of the testes forms an interesting chapter in embryology. Peculiarly, if the testes are transplanted to the abdomen, as in experimental procedures, or if, as in this case, there is failure to descend, atrophy of the gonad results.

Failure of development of the testes has certain specific effects on the organism as a whole. The external genitalia remain small. The persistence of lanugo without growth of the beard, pubic and axillary hair, the high-pitched voice, failure of the psychic development, and the skeletal proportions are all attributed to dysgenitalism. The long bones continue to grow as a result of the failure of ossification of the epiphyseal cartilages, thus resulting in a preponderance of the lower length over the upper. The upper extremities, due to their increased length, ap-

proach the lower and the span approaches and exceeds the total height of the body. This disturbance of the normal skeletal proportions differs from that of the thymus syndrome in that the overactive or persistent thymus tends to increase the torso length. Sajous, who has summarized the functions of the gonads, is of the opinion that they determine the time of closure of the epiphyseal lines in the long bones, and, second, they determine the development of the secondary sex characteristics, physical and mental.

The posterior lobe of the pituitary gland secretes a substance that acts directly on the smooth muscles. This is observed clinically after the administration of pituitrin by such manifestations as increased intestinal peristalsis and uterine contractions. Conversely, in hypopituitary states, constipation and dysmenorrhea are the symptoms that frequently bring the patient to the physician. The pressor effect of pituitrin as manifested by a rise in blood-pressure is not considered a direct effect on the blood-vascular system, but rather an indirect action through the stimulation of the adrenal body. The carbohydrate metabolism, at one time considered a function of the posterior lobe, is now considered to be either directly or indirectly related to the pars intermedia. The anterior lobe plays its greatest individual rôle in the skeletal growth of the body. In this respect, however, it differs from the gonads and the thymus in that it stimulates the growth of the flat bones. Hyperactivity, or perverted activity of the pituitary gland, if manifested before the age of puberty, results in giantism; after puberty the picture is that of acromegaly. Hypo-activity of the gland before puberty results in a retardation or cessation of the growth, with a clinical picture of dwarfism, and a retention of the childish facial features. The face is round and fat, and without maturity. The eyebrows are placed in the middle of the height of the head, and the normal adult proportion of face to skull (4 to 3) is not maintained. The hands and feet are small, chubby, and dimpled.

Although the exact relation between the gonads and the hypophysis has not been determined, many instances, suggesting an association between the two, are given. Von Eiselsberg, Goetsch,

Marinus, and numerous others have noted that the feeding of pituitary substance to animals stimulated the sex glands. Houssay has shown that dogs who survive hypophysectomy have a retarded gonadal development. In adults, testicular atrophy has been observed by Cushing in cases of extensive lesion of the whole gland, or of the anterior lobe alone. A number of investigators, the pioneer of whom was Fichera, have observed the effect of castration upon the hypophysis. Their observations would show that when an animal is castrated, there is hypertrophy of the anterior lobe, together with a hyperplasia of the eosinophilic cells. There is clinical evidence to support the view of a close relationship between the gonad and the pituitary gland. The severe headaches, experienced by some patients during menstruation, are explained as a result of increased intrasellar tension due to the increased activity of the hypophysis at this time. Some patients give a history of severe headache with nausea during and immediately following coitus.

The metabolism of carbohydrates, together with the storage of fat, is a distinctive feature of dyspituitarism. Increased tolerance for carbohydrates is an established fact in cases of hypopituitarism, while hyperpituitary states, as acromegaly, present the picture of decreased tolerance, with a tendency to glycosuria. Since the discovery of insulin, the theories regarding carbohydrate metabolism have been supported in part by clinical observations. Nevertheless, those cases of acromegaly with a high blood-sugar and showing transient melituria, thus presenting a laboratory picture in accord with diabetes mellitus, have been little understood. Cushing has observed that in such cases the glycosuria tends to disappear on insulin therapy. Partial hypophysectomy in a majority of his cases was followed by a distinct drop in the blood-sugar curve. He would explain the relation between the internal secretion of the islets of Langerhans and the pituitary as antagonistic; that, in an oversecretion of the pituitary gland, there is either a depression of the islet activity or a chemical neutralization of insulin and, conversely, a hyposecreting hypophysis would result in increased insulin production with a consequent increased sugar tolerance.

The basal metabolism of (—) 22 per cent. would at once direct attention to a hypothyroid condition. As a matter of fact, the thyroid gland is considered by most observers the most common associated endocrinal derangement of gonadal insufficiency. The enlargement of the thyroid gland during pregnancy, the dysmenorrhea associated with Graves's disease, the infantile gonads of cretinism, and the impotence in hypothyroid states are not infrequent suggestive signs of an existing relation between these structures. Various clinics are reporting favorable results with thyroid therapy in those women who present the syndrome of lassitude, asthenia, amenorrhea, gain in weight and a slightly decreased basal metabolism. The gonadal insufficiencies associated with hypothyroidism may be considered as part of the generally lowered metabolism. However, the thyroid insufficiency, secondary to the hypogenitalism, is as yet an unknown quantity. The sluggishness, the lowered body temperature, the myxedema, and the lateral, superciliary thinning of the hypothyroid are absent in this case.

The eosinophilia seen in some endocrinopathies is interesting. The tendency to an increased blood eosinophilia has been observed in thymic states and adrenal disease. A relationship between the eosinophilic cells in the anterior lobe of the hyperfunctioning pituitary gland and the blood eosinophilia in other endocrine states is suggested. In the vicinity of New Orleans, a blood eosinophilia immediately suggests parasitic intestinal infestation, and such possibilities must be ruled out. In this case, as well as in others which have come under my observation, the stools were negative for ova and parasites. Likewise, other conditions, as asthma and certain skin lesions, must be eliminated. Suffice it to say that the true nature of the eosinophilic cells and their function in the human economy has, as yet, not been determined.

Therapy.—The one hope in cases of hypofunctioning endocrine glands is in opotherapy. The results obtained are quite variable and at times entirely unsatisfactory. On the other hand, in some of the cases of endocrine insufficiencies, most spectacular results are had. In this regard, we have only to be

reminded of the dramatic transformation of the cretin to a normal adult on minute doses of thyroid extract. Less dramatic, but just as gratifying results are obtained with pituitary gland substance in those cases of combined ovarian and pituitary insufficiencies. Unfortunately, the testicular hormone has not been isolated, and the results from administration of the extract have been variable. Our patient has been on 130 mg. of whole pituitary gland three times a day for the past two weeks. He says he feels better, and the headaches have practically disappeared. There has been little, if any, amelioration of the tremors and the stiffness. We propose to continue the pituitary extract for another two weeks, check all our findings and then add testicular extract.

In an individual of this age showing such a marked anatomic gonadal deficiency a great deal can not be anticipated.

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THE VALUE OF RED CELL DIAMETER ESTIMATIONS IN ANEMIAS

DURING the past year, while working in the white male clinic of the Charity Hospital with Professor J. H. Musser, we have been very forcefully impressed with the relatively large number of patients visiting the clinic for one complaint or another who have an apparent and often striking anemia. We have, therefore, been on the lookout for all cases of anemia, and have investigated and followed all such cases rather closely.

The chief immediate indication, after determining that the patient has an anemia, is to investigate the case for a possible cause, or, in other words, to decide whether the anemia shall be placed in the classification of primary or secondary anemia.

This is very often a difficult task and one must need use every examination at his disposal to establish a definite diagnosis. To complicate the situation further, we have been seeing recently quite a few cases of sprue, and the differentiation of sprue and pernicious anemia, if they be two separate clinical entities, is often apparently impossible.

Because of our difficulties and the frequency with which we were seeing all sorts of grave anemias, I began to make studies on the diameter of red blood-cells, and the variation in the average diameter of the red blood-cells in the different types of anemias. This work was initiated by Price-Jones.[1] Since his work, many clinical observations have been made with this method of measuring the diameters of red blood-cells in various blood dyscrasias.

The work of Price-Jones furnished an accurate, practical, clinical method to corroborate the observation, which is of long

standing, that a large percentage of the red blood-cells in pernicious anemia were cells larger than normal, megalocytes; the anemia being frequently termed for this reason "megaloblastic." My observations were made following the technic outlined by Grosh and Stiefel,[2] and a brief description of the method may be warranted here.

An ordinary, well made, dried blood-smear is used, and is stained with Wright's stain. The cells are measured in the thin, one-layer portion of the smear, where they are fairly well isolated from one another. Only round cells are measured, and these only in one diameter. Two hundred cells are measured and the numerical average diameter then determined. The measurements are plotted on graph paper, as described below, and a curve made, which curve is of considerable diagnostic value. The measurements are made with an ocular micrometer. This is an ordinary ocular, and contains a glass disk on which is an arbitrary scale. This scale is calibrated for the lenses and tube length of the microscope to be used, by means of an object micrometer. The micrometer is a slide on which are divisions of known value. By focusing the image of the divisions of the ocular scale on the image of the divisions of the object micrometer, using the oil immersion lens, the value of the ocular divisions is determined for the oil immersion lens and the tube length giving a proper focus. These values are in microns (μ) and therefore, knowing the value of the ocular divisions, the stained blood-smear is focused, and the cells lying on the scale are measured. The slide is moved, and cells in focus measured again, so proceeding across the slide until 200 cells are measured. The graph is constructed by plotting the diameter of the cells in microns on the ordinate, and the number of cells of the different diameters on the abscissa. The curve is formed by joining the points on the graph paper by straight lines. The average normal red-cell diameter has been established by various observers as being between 7.18 and 7.7 μ, with a fairly characteristic graphic curve. Pernicious anemia shows a most striking picture, the average diameter being always larger than normal, with marked variation in the diameters of the cells. In secondary anemias the

average diameter is always well within normal limits, or smaller than normal, and the curve is sometimes quite striking, though seldom characteristic.

The value of such an examination is of course quite apparent, and various individuals, using this method of determining the average diameter of the red cells, have substantiated the observations that the average red-cell diameter is always increased in pernicious anemia, and normal or decreased in secondary anemias.[3, 4, 5, 6] The increase in size when accurately determined is of diagnostic importance, therefore, in differentiating between pernicious anemia and other types of anemia. Very few observations have been made upon the red-cell diameter in sprue,[7, 9] and the findings in such cases are interesting, inasmuch as I have found, as have others previously, that the average red-cell diameter is increased in sprue, and that this method offers no assistance whatsoever in the differentiation of sprue and pernicious anemia.

The similarity of sprue and pernicious anemia is increased by these observations on the size of the erythrocytes, therefore the difficulties in differentiation shall be mentioned, and the few occasional dissimilarities between the two conditions enumerated.

The close resemblance of sprue and pernicious anemia has attracted considerable attention recently, and has occasioned several writers to venture the supposition or suggestion that the two diseases, now considered clinical entities, are but different manifestations of the same condition. Wood[9, 10] stresses the relationship of the two and reports having found Monilia psilosis in the stools and on the gums of a series of cases of pernicious anemia, the Monilia psilosis being considered by Ashford[11] as the specific causative agent of sprue. Warthin,[23] in a recent article, states that he has not been able to confirm Wood's work as to the specificity of the Monilia psilosis, and reports no changes in the blood-counts, nor, pathologically, in guinea-pigs and rabbits given cultures of Monilia psilosis orally and intravenously. Wood[9] states that he is unable to make a clinical differential diagnosis of sprue and pernicious anemia after

fifteen years study of sprue. Musser[12] discusses the similarity and probable relationship between the two conditions. Elders[4] comments on the similarity, and states that the only real differences he has been able to observe is that the gastro-intestinal symptoms are usually more serious in sprue, and may be absent in pernicious anemia. Gastro-intestinal fermentation, with the production of acid stools and gas, is more marked in sprue, and there is usually a higher degree of emaciation in sprue than in pernicious anemia.

The usual blood changes in sprue are similar to those in pernicious anemia with a more or less marked anemia and a high color-index. There is an increase in the average size of the red blood-cells, and the curves of the diameter of the cells obtained have been similar to those of pernicious anemia. In both, a diarrhea and glossitis are common, and sprue progresses with remissions as much as does pernicious anemia. For quite a long while it was considered that the achlorhydria of pernicious anemia, occurring in about 92 per cent. of cases,[13] was a very important point of differential diagnosis, but there have been several cases[14, 15] reported of undoubted pernicious anemia, some with necropsy, with free hydrochloric acid present. Still other authors maintain that all cases of pernicious anemia show an achlorhydria, and that this finding is essential for a proper diagnosis. Levine and Ladd,[15] in an analysis of 107 cases, found that all but three, 99 per cent., showed no free hydrochloric acid, and state that its persistent presence throws doubt upon the diagnosis of pernicious anemia. Willson and Evans,[16] in an analysis of 111 cases, found that none showed free hydrochloric acid. Others cite cases showing that the achlorhydria very often precedes the onset of the symptoms of pernicious anemia by many years. It has been considered as being responsible for the production of the disease.[18, 19] It is true that apparently achlorhydria does not occur so frequently in sprue as in pernicious anemia, but the fact that it does occur further confuses the picture.

Because of the frequency of achlorhydria, Hurst[19] wisely recommends that every case with achlorhydria should have a careful examination of the blood for megalocytes, and that a test-

meal should be given to every patient with a sore tongue or paresthesias, because they are often the earliest symptoms of pernicious anemia.

The cord changes of pernicious anemia have also been a sheet-anchor in the differential diagnosis. While the occurrence of subacute combined degeneration of the spinal cord is a very valuable differentiating sign of the disease, confusion may arise, because Elders[4] reports a case of sprue with ataxia and anesthesia of both legs and sluggish knee-jerks, and Wood[10] states that the nervous system does not always escape in sprue. Hurst[18, 19] notes that 80 per cent. of cases of pernicious anemia show cord changes sometime during the course of the disease. Reese and Beigler[20] write that 80 per cent. of their cases of pernicious anemia showed some neurologic manifestation. These cord changes often precede the characteristic blood-picture, and are, therefore, of utmost importance and significance. Incidentally, however, the average red-cell diameter is said to be increased even in such early cases of pernicious anemia. Subacute combined sclerosis is always associated with an achlorhydria and never associated with a secondary anemia (Hurst). These cord changes may occur, however, in arteriosclerosis, pellagra, and apparently in other conditions.[10]

The state of nutrition of the patient in pernicious anemia has always been described as of importance; that the patient is usually well-nourished, out of proportion to the anemia, with the preservation of considerable body fat. Willson and Evans[16] report 39.6 per cent. of their cases as poorly-nourished, and 60.3 per cent. as well-nourished. The individuals with sprue are usually poorly nourished or emaciated, depending upon the duration and severity of the condition, but most of those cases of pernicious anemia seen in the clinic have showed a marked degree of emaciation.

In many instances all that one may accomplish is the differentiating of an anemia into a primary or a secondary group, or, as Hampson and Shackle suggest, megalocytic and non-megalocytic anemia, which seems at present to be the most satisfactory separation or division. This separation can only be

made with definite accuracy by measuring the red blood-cells, the method described previously being probably the simplest. An anemia of the megalocytic type will be due to pernicious anemia, sprue, or dibothriocephalus infection, no other anemias apparently giving such pictures by this method. The enlargement of the cell continues through the disease, even in remissions apparently, though Medearis and Minot[21] have recently made observations from which they conclude that the average size of the cell diminishes and approaches normal in pernicious anemia cases treated with the high purine diet of Minot and Murphy,[22] but then only when the total erythrocyte count has reached a level of 4,200,000 or above. Recently we had a case of undoubted clinical pernicious anemia with a marked anemia and hemoglobin of 25 per cent. whose average red-cell diameter was 7.97 μ. This patient died two days later, and the approach of the average diameter to normal would suggest the probability that this occurs as the bone-marrow becomes aplastic, and that it is of considerable prognostic importance when the change can be followed. Further observations will be very interesting in this respect.

It should also be pointed out how frequently the blood-picture of a known secondary anemia approaches, in so many characteristics, the blood-picture of the primary or pernicious anemia. The color index is often 1.0 or higher with marked anisocytosis and poikilocytosis and very often nucleated red cells. The one differentiating point is the alteration in the size of the red cell, as stated above.

The clinical value of the examination and measurements may now best be shown by citing a few case histories with the problems they presented.

Case I.—H. D., a white male, fifty-five years of age, was admitted to the clinic on October 13, 1926. His weight on admission was 122 pounds. His complaint was of pain in the epigastrium, which had been first noticed about two years previously, lasting about one week at that time. It then disappeared, to reappear about one month ago. The pain was brought on

by exertion, and also occurred both during and after meals. He also had had bleeding hemorrhoids for the past twenty years, and a slight cough for several weeks, also dyspnea upon exertion. There were no other complaints. The past history was of no importance.

Physical examination showed a markedly anemic, quite nervous, deaf individual who was well developed and well nourished. Blood-pressure was: systolic 130, diastolic 80. The pupils were equal, and reacted both to light and accommodation. The teeth were in poor condition. The mouth and tongue were negative. The heart and lungs showed no demonstrable abnormalities. The spleen border was easily palpable about three fingers below the left costal margin, and the liver margin was palpable about two fingers below the right costal margin. There was no edema of the lower extremities. The patellar reflexes were active, and no abnormal reflexes could be elicited. The epitrochlear glands were palpable on both sides. On October 13th, the hemoglobin was 30 per cent., total erythrocytes 3,000,000, and total leukocytes, 6000, of which 68 were neutrophils, 31 small lymphocytes, and 1 large lymphocyte. The blood-smear showed anisocytosis and poikilocytosis, and no malaria plasmodia were found. The Wassermann reaction on the same date was negative, as was also the urinalysis. An Ewald test-meal showed free hydrochloric acid of 25, and a total acidity of 80. The examination of the stool showed no ova or parasites. Rectal examination showed no external hemorrhoids. On the same date the average red-cell diameter was 6.3 μ. On October 18th the hemoglobin was 30 per cent., total erythrocytes, 3,100,000, and total leukocytes, 6000, of which 66 were neutrophils, 28 small lymphocytes, 4 large lymphocytes, and 2 eosinophils. The examination of stool again showed no abnormalities. The fragility test showed that hemolysis began at 0.38 per cent., and was complete at 0.30 per cent. The van den Bergh on October 21st was negative, both in the direct and indirect reaction. Gastro-intestinal roentgenograms on October 22d disclosed no abnormalities. A repeated van den Bergh reaction on October 25th was, again, negative both in the direct

and indirect reaction. Another average red-cell diameter estimation done on October 25th was 6.87 μ. On November 3d the hemoglobin estimation was 40 per cent., on November 5th the hemoglobin was 45 per cent. The patient began to cough up blood-tinged sputum on November 10th, but careful examination of his lungs failed to give any evidence of pathology. Sputum examinations were made, and roentgenograms of his chest requested, and on November 19th the Roentgen-ray report showed pulmonary tuberculosis of both apices, and acid-fast bacilli were found in his sputum. At this time bronchovesicular breath sounds were demonstrable at both apices. The hemoglobin on this date was 65 per cent. Hemoglobin estimation on December 3d was 75 per cent., with a total erythrocyte count of 4,800,000. On December 27th the patient's hemorrhoids began to bleed quite severely, and on January 3d he was referred to the surgical clinic for treatment of this complaint. His weight at this time had risen to 134 pounds.

Discussion.—This quite apparently anemic patient presented a very interesting problem. The anemia associated with the marked splenic and hepatic enlargement suggested several possibilities. The history of epigastric pain also complicated the picture. Among the possibilities thought of were: Pernicious anemia, Banti's disease, secondary anemia associated with hepatic malignancy or cirrhosis of the liver, and syphilis. The history of the case gave nothing to suggest sprue. The blood-examination was the first made, and the color index of 1.0+ might have furthered the probability of pernicious anemia, along with the marked anisocytosis and poikilocytosis. The red-cell diameter estimation, however, showed an average diameter of 6.3 μ, which according to all previous observations placed the anemia well within the secondary group, or better, within the group of non-megalocytic anemias.

Subsequent investigations, as shown, substantiated this classification. The free hydrochloric acid of 25 did not favor the diagnosis of pernicious anemia. The history of bleeding hemorrhoids for many years and the occurrence of severe hemorrhages from this source, while under observation, with the associated

hepatic enlargement, warranted the diagnosis of cirrhosis of the liver with bleeding hemorrhoids, producing the secondary anemia. Later examinations showed the presence of pulmonary tuberculosis as recorded, which had undoubtedly added to the condition, but which I do not think was entirely responsible, being apparently of only a comparatively recent date in its activity.

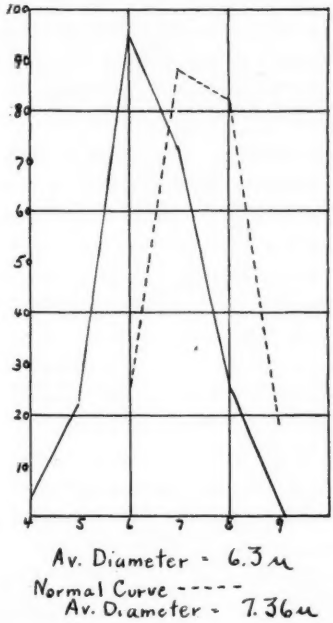

Fig. 195.—Case I. H. D. Secondary anemia.

The graph shown below is typical of a secondary anemia, the curve being displaced well toward the left of the normal curve, which is superimposed for comparison. This is as characteristic as is the average size of the erythrocytes.

Case II.—J. B., fifty-six years of age, a white male, complaining of dyspnea and fulness in the epigastrium, was admitted on November 17, 1926. His illness had begun a few months pre-

viously when he began to notice dyspnea and palpitation, which had not been associated with pain. For an indefinite time he had also been having diarrhea with loose watery movements two or three times daily, and occasionally as many as seven or eight times a day, these movements sometimes being frothy. Some edema of the ankles had also been noted for about one week previously. His weight upon admission was 115½ pounds. The past history was of no importance. Upon physical examination one noted the striking pallor of the patient, and the fact that he was quite poorly nourished and developed. The tongue was red, clean, and smooth. Examination of the heart and lungs did not show any abnormalities. The abdomen showed no pathology. The extremities likewise were negative. Blood examination showed the hemoglobin to be 45 per cent., total erythrocytes were 1,385,000, with a color index of 1.5. The total leukocytes were 9500, and the differential count showed 76 neutrophils, 18 small lymphocytes, 5 large lymphocytes, 1 eosinophil, and rather marked anisocytosis and poikilocytosis. The average red-cell diameter was found to be 9.4 μ. An Ewald meal showed free hydrochloric acid of 35, and a total acidity of 110. Urine examination reported a trace of albumin and a few pus-cells. The feces were yellow and frothy, and, except for undigested food particles, was negative. The patient was admitted to the hospital wards on November 22, 1926, and discharged December 20, 1926. On January 28, 1927 the hemoglobin was 60 per cent., and the total erythrocyte count, 3,900,000; the patient was feeling very much better. The Ewald meal on February 11th showed free hydrochloric acid of 50, and a total acidity of 100. On April 1st the hemoglobin was 70 per cent.

Discussion.—The complaint of a fairly long standing diarrhea in this case, with the presence of an apparent anemia, and a very characteristic, smooth tongue suggested immediately either sprue or pernicious anemia. It is to be noted, however, that the symptoms which distressed this patient most were those of the anemia, chiefly the shortness of breath and weakness. The bowel movements were said to have been frothy at intervals. On the other hand, might not such a picture, in an individual fifty-six

years of age, have been the result of a malignancy? There was no history of pain of any sort, and no history of gastric disturbances, except a sense of fulness in the epigastrium.

The blood examination showed the high color index of 1.5. Knowing that secondary anemias at times produce similar high color indices, I do not consider this sufficient evidence to warrant the opinion that such an anemia is primary. The average red-

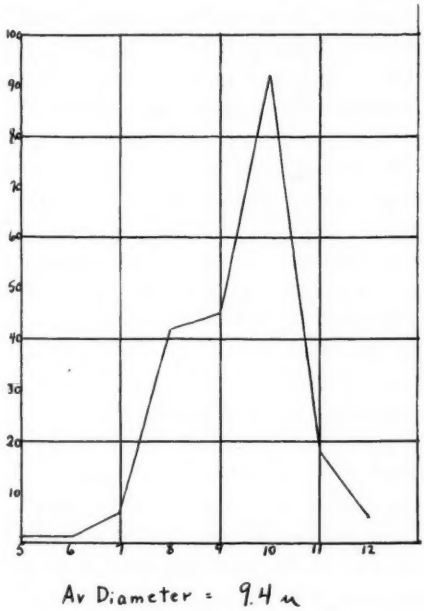

Fig. 196.—Case II. J. B. Sprue.

cell diameter was found to be 9.4 μ, and I then considered the condition sprue or pernicious anemia from these findings. Subsequent examinations showed free hydrochloric 35, and, later, free hydrochloric acid 50, which along with the character of the diarrhea was thought to warrant a diagnosis of sprue. While in the Hospital he was given a sprue diet, one rich in carbohydrates, especially bananas, receiving 6 to 8 or more bananas each day,

which diet he is still observing. His improvement has been progressive.

The graph of the first measurements is shown. Subsequent measurements showed an average diameter of 8.73, 9.1, 8.44, and 8.8 μ, respectively.

Case III.—H. B., a forty-eight-year-old white male, was admitted on November 26, 1926, complaining of indigestion and swelling of his feet. The onset had been six months previously with heaviness and belching after eating, and some occasional sour eructations. Two months previously he had first noticed edema of his ankles, and this had persisted to the date of his first visit. His mouth had been sore at intervals since the onset of the condition, and the bowels had been moving 4 or 5 times each day. These stools were often watery and loose, light yellow or green in color, and said to be frothy occasionally. There were no other complaints. The past history was irrelevant.

Upon physical examination one was struck immediately by the light yellow pallor of the patient. There was marked pallor of the conjunctiva and oral mucous membrane. The pupils were equal and reacted to light and accommodation. The mouth was sore, the tongue being bright red and smooth. The teeth were in poor condition. No abnormalities were detected upon examination of the heart and lungs. The liver was palpable 3 cm. below the costal margin, though not tender on pressure. The ankles showed pitting edema. The patellar reflexes were active, and no abnormal reflexes were elicited. The vibratory sense was preserved. His systolic blood-pressure was 108, and the diastolic pressure, 68. The patient's weight upon admission was 133½ pounds. His blood-picture on November 29, 1926 was: Hemoglobin, 45 per cent.; total erythrocytes, 2,140,000; total leukocytes, 5500; the color index being 1.07. In the differential count there were 55 neutrophils, 30 small lymphocytes, 1 large lymphocyte, and 14 eosinophils; marked anisocytosis and poikilocytosis, but no nucleated red cells. The average red-cell diameter was 8.12 μ. Urinalysis showed no abnormal changes on repeated examinations.

The Wassermann reaction was negative. Two Ewald test-meals were given the patient; the first showed no free hydrochloric acid, and a total acidity of 7; while in the second meal, given on December 1st, there was a free hydrochloric acid of 3, and a total acidity of 38. On January 31, 1927 the hemoglobin had risen to 50 per cent., the erythrocyte count was 1,500,000.

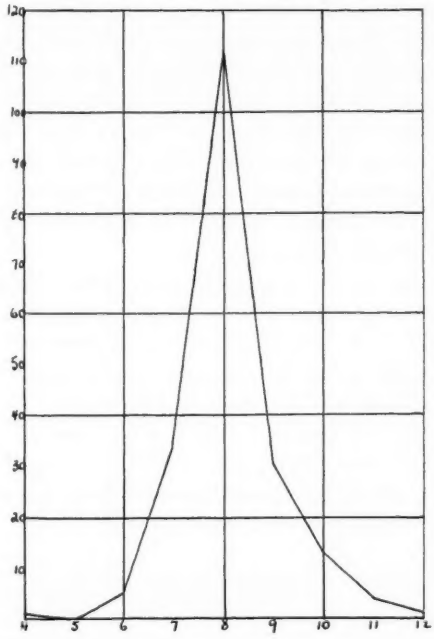

Fig. 197.—Case III. H. B. Pernicious anemia.

Feces examination on February 14, 1927 showed the presence of strongyloids. The patient was admitted to the hospital on February 23, 1927 and was discharged on April 4, 1927. When seen in the clinic again on April 6, 1927 he was much stronger, the color much better, hemoglobin 80 per cent., and the weight had increased to 150 pounds, a gain of $16\frac{1}{2}$ pounds. The liver feeding had been begun on January 31, 1927.

Discussion.—This case showed marked anemia, associated with diarrhea said at times to be frothy, enlargement of the liver, and smooth tongue. The color index was 1.07. The red-cell diameter, however, was well above normal, being 8.12. There was no loss of vibratory sense, no other cord changes. The gastric analysis of no free hydrochloric acid, and later a free hydrochloric acid of 3, could have been taken in association with either the diagnosis of sprue or pernicious anemia. The patient was considered to be one of pernicious anemia, the diarrhea never, while under observation, assuming the frequency or characteristics of that of sprue, and as such was placed on the high protein diet as suggested by Minot and Murphy.[22] On this regimen his improvement was quite marked, though not until he was admitted to the hospital where the regimen could be followed strictly as ordered.

In this case, as in Case II, the therapeutic improvement on different diets was considered as being probably one of the best indications as to the correctness of the differential diagnosis between sprue and pernicious anemia. Certainly, in neither case was there any definite criterion to differentiate the two conditions, and there were many points similar to each.

Subsequent measurements were 8.68 and 8.61 μ, there being no apparent relation in either Case II or Case III between the size of the cell and the improvement noted.

Case IV.—H. L., a white male, sixty-four years old, was admitted to the clinic on November 12, 1926, complaining of loss of weight and anorexia. He weighed 116 pounds on admission, and stated he had begun to lose weight about one month previously. The onset of the condition seemed to have been with a cold which had lasted for about one week, following which he had had no appetite, was nauseated at times, and had to force himself to eat. He had lost about 35 pounds since the onset one month previously. He had had a very severe cough during the cold, which had disappeared entirely. Upon questioning he complained of pain in the upper abdomen after eating, with vomiting often almost immediately after eating. There was no history

of constipation or diarrhea, but he stated he had had bleeding hemorrhoids for many years. There were no other complaints. The past history was apparently of no importance.

Physical examination showed a well developed, though very poorly nourished, and markedly anemic, white male. The blood-pressure was systolic 90, diastolic 55. The eyes showed no apparent pathology. The heart and lungs were apparently normal. The abdomen showed no abnormalities except a bilateral, inguinal hernia. The patellar reflexes were active, and there was

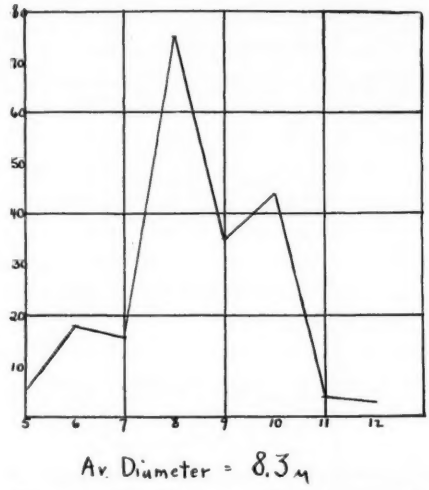

Fig. 198.—Case IV. H. L. Pernicious anemia.

no loss of vibratory sense. On November 15, 1926 the hemoglobin was 35 per cent.; the total erythrocytes, 1,535,000; the total leukocytes, 3500, of which 60 were neutrophils, 38 small lymphocytes, and 2 large lymphocytes. Anisocytosis and poikilocytosis were present. The Wassermann and urinalysis were negative. The Ewald test-meal showed no free hydrochloric acid, and a total acidity of 12. On November 22d, a gastro-intestinal series showed no definite evidence of stomach pathology.

Discussion.—This case, unfortunately, is not a complete record, because the patient was lost track of, and further observations could not be made. It offers some interesting considerations, however. With the complaint of pain in the upper abdomen in an individual sixty-four years of age, associated with the loss of 35 pounds of body weight in one month, vomiting at intervals, and marked anemia, the diagnosis of gastric carcinoma is worthy of serious consideration. The color index was 1.1, and the red-cell diameter, 8.3. This latter observation would place the condition outside of the secondary group, and, if all observations which have been made and which have been constant are to be considered and accepted, would definitely rule out the diagnosis of a secondary anemia due to gastric carcinoma. The extreme value of such an examination cannot be overestimated. Subsequent gastric analysis showed no free hydrochloric acid, and the gastro-intestinal series showed no definite evidence of stomach pathology. During one week of hydrochloric acid therapy with Blaud's pills, the patient was feeling much better. The diagnosis of pernicious anemia was made on this case, with the realization that further observations would have been greatly desired.

It is interesting to note the history of bleeding hemorrhoids for many years in this case, which was probably only a secondary consideration.

Case V.—J. G., a white male, sixty-nine years old, weighing 139 pounds, was admitted on January 24, 1927, complaining of chronic constipation and abdominal pains with weakness. He had been constipated for very many years, and for several years had been having vague, general pains over the abdomen. Since the previous December, following an attack of influenza, he had been worse, growing progressively weaker. Since that time he had lost considerable weight, and had had quite severe pain in the left side of the abdomen, which felt like something tight. There was no history of diarrhea, and no other complaints.

Physical examination showed a poorly nourished, slightly anemic individual. The pupils were equal and did not react to

light. The teeth were in poor condition. The pulse was irregular from premature contractions. The lungs were clear. The heart showed no abnormalities except the irregularity. The abdomen was tense and rigid. A mass was palpated on the right side below the costal margin, 8 cm. below the costal margin in the midclavicular line, tender on pressure, hard and distinctly nodular. This mass extended to the left side beyond the mid-

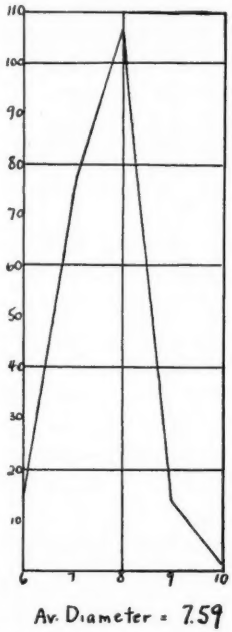

Fig. 199.—Case V. J. G. Carcinoma.

line. The Wassermann was negative. Roentgen-ray examination showed a constant and persistent filling defect, no evidence of tumor mass, enlarged liver, and increased density, the report stating that the plates were suggestive of a malignancy of the stomach.

Discussion.—Here are the symptoms of a chronic constipation and abdominal pains, with considerable loss of weight, and

anemia, in an individual sixty-nine years of age. The abdominal examination showed a mass, apparently the liver, occupying the greater portion of the abdomen, as described. The tentative diagnosis of hepatic malignancy was made, and syphilis was considered a possibility inasmuch as his pupils did not react to light.

The red-cell diameter of 7.59 was in keeping with the diagnosis of a secondary anemia, whether due to a syphilitic or malignant involvement of the liver. However, the gastro-intestinal series, with the report of a suggestive malignancy of the stomach, furthered the latter diagnosis.

It is to be noted that the red-cell diameter in secondary anemias is never increased above the normal averages, being either well within normal limits, as in this case, or definitely below the average normal, as in Case I.

Case VI.—M. H., a white male boy, thirteen years of age, was admitted to the clinic February 23, 1927, complaining of weakness and nausea in the mornings. For several weeks previously the patient had been feeling weak and nauseated after breakfast, not occurring every morning, only occasionally. The discomfort would last only a few minutes, and was not associated with any discomfort; no vomiting. The boy stated that in addition to this discomfort, he wanted to be examined because he was not as large or as heavy as other boys his age. He had grown very little during the past few years, and two years ago weighed the same as he weighs at present. The appetite was good, though the bowels were constipated. He had been having frontal headaches occasionally. There were no other symptoms. As a child he had had only measles.

The physical examination showed a small, poorly developed, poorly nourished, anemic boy. No abnormalities whatsoever were noted, except the very apparent anemia of the conjunctivæ, oral mucous membranes, and nail beds. On February 25, 1927 the total erythrocytes were 4,810,000; the total leukocytes, 4500; and the hemoglobin 60 per cent. The Wassermann reaction was negative. On March 9th the hemoglobin was 75 per cent., and

on March 30th the hemoglobin had risen to 80 per cent. Urine and feces examinations showed no abnormalities on repeated examinations.

Discussion.—This is presented as a rather common type of secondary anemia, with the average red-cell diameter of 7.6 being well within normal limits, and in keeping with this diagnosis.

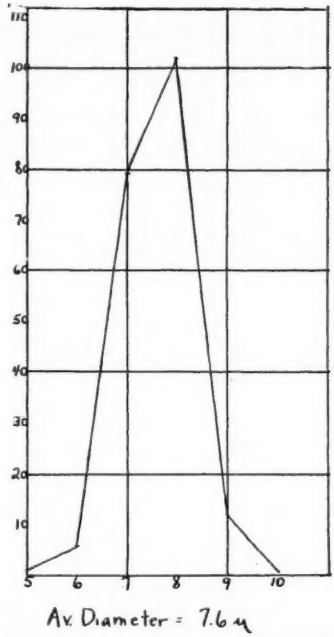

Fig. 200.—Case VI. M. H. Secondary anemia.

The anemia was apparently due to improper diet and nutrition and is improving progressively under proper diet and Blaud's pills.

Case VII.—L. G., a white male, seventy-two years of age, weighing 101½ pounds, was admitted complaining of cramp-like feeling in the legs, dizziness, and indigestion. The illness had begun about one year previously with indigestion. He had had

no appetite. There was no associated pain, and he had been on a restricted diet. The exact nature of this gastric disturbance could not definitely be determined. At the time of his visit the gastric discomfort was no longer present, and the cramps in his legs bothered him most. These had been present for about ten months. The appetite was poor, and the bowels were moving 4 or 5 times a day, very loose and watery. He had vertigo and palpitation on exertion, but no other symptoms. The past history was irrelevant. Upon physical examination one noted

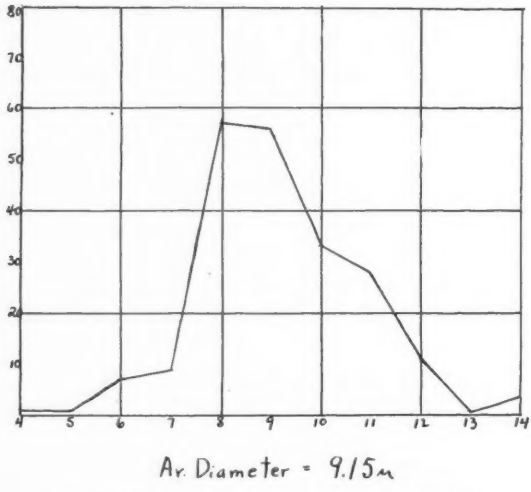

Fig. 201.—Case VII. L. G. Pernicious anemia.

an anemic, poorly nourished, thin, poorly developed, white male. Thorough examination failed to show any abnormalities. He was admitted to the hospital on February 14, 1927. On this date the average red-cell diameter was 9.15 μ. The total erythrocytes were 1,835,000; hemoglobin 40 per cent.; color index 1.1, and an occasional nucleated red cell was noted. He gained 14 pounds on the liver diet in two weeks. On February 21, 1927 his hemoglobin was 55 per cent.

Discussion.—This case is presented as a typical case of per-

nicious anemia, with a red-cell diameter graph which is quite characteristic. The average diameter is 9.15 μ, the color index being 1.1.

It is to be noted that most of the cases of pernicious anemia, seen during the past year, have been poorly nourished, and in some cases, quite emaciated. This, as stated before, is in contradiction to the statement usually made as to these individuals being very well nourished and preserved.

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TREATMENT OF PARESIS BY MALARIA, SODAKU, AND TRYPARSAMID

SYPHILIS first came into prominence in 1493, following the return of Columbus, when there was a rapid and wide-spread syphilization of Europe. Whether this dates syphilis in Europe is not of importance here. It is important, however, to know that during this time there was a very rapid spread of the disease throughout the entire continent. Osler states that "syphilis reached Italy in 1493, being brought in by the army of Charles VIII. His soldiers syphilized Naples; the disease spread throughout Italy, and in a few years Europe was aflame." The ravages of the disease during the following centuries are analogous to the great plagues, and the prevalence of the disease was appalling. This syphilis, as known in the fifteenth century, would hardly be recognized as the forerunner of the disease we know today. Its predilection during these early times was for the skin and its sufferers were most horrible specimens.

Progressing down through the history of this condition, we see it leaving the skin and becoming more prevalent in the bones and joints, it being a common practice to diagnose the disease by the rough, nodular feel of the tibia; still later, the vascular system was attacked, for it was not until the eighteenth century that Lancisi[19] recognized the relationship of syphilis and aneurysm. Later still do we find the nervous system the seat of syphilitic manifestations.

Prior to the advent of the Wassermann reaction in 1907,[20] and the discovery of Ehrlich's 606[20] in 1909, the diagnosis and treatment of syphilis in all its forms was sadly neglected. Since the epoch-making discovery of the specificity of arsenic for the

spirochete, each generation has added to what was previously known, until the treatment of syphilis in all its forms except neurosyphilis has become a very exacting science. In this paper I shall present to you the three most accepted therapeutic procedures used in the treatment of neurosyphilis, laying particular stress on paresis, and as the malaria plasmodia inoculation was the first deviation from the salvarsan treatment, I shall discuss it first.

In 1887, Wagner von Jauregg[2] first laid particular stress on the fact that remission in paresis often followed attacks of acute infectious diseases, and that these remissions lasted longer than did the spontaneous remissions. Working on the theory that the febrile reaction was directly the cause of the remission, he used foreign substances to produce a moderately severe febrile reaction. He first used injections of 0.1 gm. of Koch's old tuberculin, and in 1909 reported favorable results from this type of treatment in a paper read before the International Medical Congress, and again discussed the possibilities of using malaria inoculation, stating that in this way a febrile reaction which was easily controlled might be obtained. His idea did not meet with wide-spread approval, and it was not until 1917[1] that he reported his first case treated by malaria inoculation. During the span between 1909 and 1917 von Jauregg used tuberculin with mercury, Besredek's[3] typhus vaccine, and other mild fever-producing agents with which he was able to produce some favorable results, but which he did not consider satisfactory. Von Jauregg was supported in his theories by Pilcz[4] whose work was closely related to that of the pioneer von Jauregg.

Shortly after von Jauregg published his paper expressing the malaria-inoculation theory, Bercowitz,[5, 14] writing from Hainon, China, reported a population of 3,000,000, of which 90 per cent. were infected with malaria. Syphilis was also practically universal, and, yet, in eight years he had not seen a single case of paresis, and only two or three of tabes. Stimulated by this report, Mattansche and Pilcz, in 1913, analyzed the histories of 4134 Austrian Army officers who had become infected with syphilis. From these histories, which was more concrete evidence

than had previously been presented, it was pointed out that, of these patients, those who developed an acute febrile disease, such as pneumonia, typhoid, malaria, or the like, during the first year of their syphilis did not develop neurosyphilis in the later course of their lives. On the contrary, those who in the later course of their lives did develop neurosyphilis, practically without exception did not have an acute febrile disease during the first year of the syphilitic infection.

On receipt of this information, and with his previous good results obtained with fever-producing substances, von Jauregg instituted the malaria-inoculation treatment, and in 1917[1] made his first report of 9 cases; 6 of which showed a complete and lasting remission, and were able to carry on their usual vocation when last seen in 1922.[17]

Technic for Malaria Inoculation.[15, 17]—Wagner von Jauregg's method of inoculation is as follows: From 1 to 4 c.c. of benign, tertian-malaria blood is injected subcutaneously, intramuscularly, or intravenously. The patient is allowed to have eight or nine chills; occasionally, ten or twelve. Quinin bisulphate is then given in doses of 0.5 gm. twice daily for three days, then once daily for fourteen days. Following the quinin treatment, six injections of neo-arsphenamin are given, beginning with 0.3 gm. and increasing to 0.6 gm., one week apart. This constitutes one series of the treatment.

Since 1917, von Jauregg[17] has treated more than 200 cases of paresis by the malaria-inoculation method, and reports the following results: 30 per cent. complete remissions, meaning a return to their previous status, both physically and mentally, where they were maintained, and were able to earn as much as prior to the onset of the disease. This series of cases, which was reported in 1922, includes not only patients with beginning dementia, but also states of severe, maniacal excitement, with delusions of grandeur and delirious reactions. He points out, however, that the earlier the treatment is started, the more favorable the prognosis. He also pointed out, in his paper of 1922, that the serology is seldom altered by this form of therapy, and states that many of his patients, though symptom-free, still gave

as strongly positive Wassermann reactions, both blood and spinal-fluid, as before the treatment was started.

In 1924, N. D. C. Lewis[15] reported the following series: 68 patients were inoculated: of these, 9 failed to take; 8 did not remain in the hospital, and all records of them were lost. Of the remaining 51, there were 16 complete remissions; in 19, the progress of the disease was arrested and remained so; 12 were not benefited, and 13 died.

In another series by Lewis, Hubbard, and Dyar the following was reported: From September 10, 1924, to March 18, 1925, 42 paretics were inoculated with benign, double, tertian malaria plasmodia. Of these, 2 failed to develop malaria, even after repeated inoculation. Of the 40 remaining, 9 died during the course of treatment or within one month following it, 3 died in from six months to one year following the treatment, 8, or 20 per cent., were in a complete remission fifteen months after the first inoculation; 4 have had remissions to the extent that they are living outside of the hospital and are earning a living; 6 have improved to a point at which they are good hospital-helpers under supervision; 2 have shown great relative improvement, having changed from a state of practical amentia to one in which they are oriented as to time and place, there has been some restoration of memory, and they are able to care for their person; 7 are unimproved.

I believe that the above figures are sufficient evidence to show that malaria inoculation is followed by favorable results in about 29 per cent. of paretics, and, if we are to accept von Jauregg's theory that the febrile reaction is directly responsible, the question naturally arises as to how such a beneficial reaction takes place. In answer to this question, I can but present the two most widely accepted theories. The first is that advanced by Jahrel,[7] in 1919. He states that the repeated high-temperature reaction produced by the malaria plasmodia is lethal for the *Spirochæta pallida*. The second, now the most accepted, is that advanced by Plaut, in 1919.[8] His theory states that there is an immunity reaction produced by the acute febrile disease, which is effective against the etiologic agent of paresis.

In both of the above theories, the main benefit derived from this form of treatment is the high temperature produced by the malaria plasmodia. The question then arises, why won't any other febrile-producing reaction serve the same purpose? As a matter of fact, as was first shown by von Jauregg, it will, but the following points have been maintained in favor of the use of malaria plasmodia instead of other fever-producing substances:

1. Frequent, recurring and high temperatures are produced.
2. The majority of the patients are susceptible to malaria.
3. The rise in temperature recurs at short intervals.
4. The disease is readily controlled by quinin.

Relapsing Fever.—Plaut,[9] in 1920, seeking to improve the malarial treatment, introduced the method of inoculating the paretic patients with relapsing fever, working on the theory that the causative agent of relapsing fever is more nearly related to the pale spirochete, that its effects on the patient were less severe, and that it could be had at all times by virtue of the fact that experimental animals are susceptible to it.

The experimental evidence, however, shows that in this condition the paroxysms of fever are likely to be separated by many weeks, that the disease is self-limited, and not infrequently before very many paroxysms have occurred; and these are very frequently of a very mild type.

Furthermore, in Plaut's own experience, arsphenamin, supposedly specific for relapsing fever, often had no effect on the disease, and the cases had necessarily to run their natural course. Many attempts to increase the virulence of the organism have failed, two or four mild attacks being the most obtained.

This evidence shows plainly that the disadvantages of this type of therapy far outweigh the advantages, and as the clinical evidence does not show beneficial results, and, furthermore, as Sodaku offers all its advantages without its disadvantages, let us turn to the latter for a febrile disease to supplant the old malaria treatment.

Spirochæta morsus muris,[11] the causative organism of Sodaku, seems to meet most of the requirements called for in the treatment of paresis by a febrile reaction. This disease is well known

in Japan, and a few sporadic cases have been reported in this country.

The infection is produced by the bite of an infected rat. At the site of the wound there appears, in from one to fifty days, a primary lesion similar to the chancre. This lesion is covered by a black, or reddish-purple scab, and is about 2.5 cm. in diameter. A lymphangitis from the sore to the neighboring glands develops, and there may appear a general adenopathy, as the spirochetes are blood-borne. Within five to fifteen days the fever occurs, and skin lesions, similar to those of secondary syphilis, cover the entire body, especially the trunk. The temperature rises from 104° to 105° F., and is of the intermittent type, falling to normal in a few hours. This rise and fall in temperature is repeated from time to time, at daily or bidaily intervals. The disease is said to be self-limited, but often continues with febrile exacerbations for months. It does, however, respond quickly to arsphenamin therapy. The disease, even when acquired from the rodent bite, usually runs a benign, self-limited course, with a very low mortality, and even in the most prolonged cases arsphenamin therapy yields excellent results.

Spirochæta morsus muris is a short, thick spiral; the curves are short and very regular. The body of the organism terminates in a point at each end, from which rises one flagellum. The spirochete was discovered by Futoki, and was shown by him to be maintained in experimental animals, and carried by the bite of infected animals to man.[10]

The material used for human inoculations consists of citrated blood taken under aseptic precautions from the heart of an infected guinea-pig or rat. This blood must first be examined by the dark-field method to ascertain the presence of the spirochetes. It is then injected into the patient intradermally.

From the obtainable experimental data, it would seem that the clinical effects produced by this spirochete offer more of the favorable and fewer of the unfavorable characteristics than do any of the other fever-producing substances thus far used. The patient's reaction is less severe than in malaria, and, for this reason, can be used in more debilitated individuals, it is

more constant and more severe than relapsing fever and thus offers greater benefits to the patient, the organism is readily maintained in experimental animals, and the condition is readily controlled by arsphenamin therapy.

With these facts before us, let us turn to a hypothetic description representing the average reaction of patients thus treated.

The diagnosis of paresis having been made by physical examination and laboratory findings, the patient is inoculated on the anterior surface of the thigh with 1 c.c. of citrated blood, taken from a guinea-pig that presents typical signs of Sodaku, and the blood of which reveals many spirochetes by dark-field examination. From the same material, two guinea-pigs must be inoculated immediately after the human injection, and must show, in the course of time, typical experimental rat-bite fever with the causative agent in their blood.

In from three to five days, at the site of inoculation, there will appear an indurated area about 1 cm. in diameter, and bluish in color, surrounded by a red areola. On the sixth or seventh day temperature of 101° to 102° F. will be found associated with inguinal, glandular enlargement, which is red and very painful, and the patient complains of general malaise and aching pains in the bones and joints. The site of inoculation will be found ulcerated and exuding serum, which will show organisms by dark-field examination.

On the twelfth to the fourteenth day, temperature of 103° to 104° F. will be encountered, which will fall to normal within three to five hours. This is associated with a gangrenous appearance at the site of inoculation and a marked, inguinal, glandular enlargement and lymphangitis. The white blood-count at this time will range from 10,000 to 15,000.

From the fifteenth to the eighteenth day a secondary eruption similar to secondary syphilis may be expected. This appears as several small, circular, well defined, elevated, ham-red spots about 1 cm. in diameter, appearing over the trunk and thighs. This eruption will be accompanied by a febrile rise to 103°–104° F., which will last twenty-four to thirty-six hours,

falling to normal, and followed by a rapid fading of the eruption.

On the twentieth day, another febrile rise to 104° F., with a reappearance of the eruption will be seen, and will follow the course of the previously described one. These febrile exacerbations may be expected at daily or bidaily intervals, but may be readily controlled by the intravenous administration of 0.15 gm. arsphenamin, which, as a rule, is begun on the twenty-eighth day, and given every three days for 3 or 4 doses. This will be followed by a rapid disappearance of the eruption, and healing at the site of inoculation. Following the administration of the initial dose of arsphenamin, a marked febrile reaction of 104° to 105° F. may be encountered, lasting for twenty-four hours, and falling slowly to normal. During the height of the fever, the patient may become delirious and excited, and have to be restrained. This may be interpreted to be similar to the so-called Herxheimer reaction or therapeutic shock seen in the treatment of syphilis during the secondary, eruptive stage, and may be treated as such.

The above constitutes one course of treatment, and, while not followed by seriologic improvement, will in 22 per cent. of the cases be followed by marked mental and physical improvement.

It is obvious that the foregoing discussion is not applicable to cases not resident in a hospital or an institution. In view of that fact, and in view of the fact that the general practitioner will no doubt be called on to treat some of these cases in their homes or in his office, I do not think it amiss to give brief consideration to the results obtained using the latest arsenical preparation, namely tryparsamid.

Tryparsamid[18] is sodium N-phenylglycinamid-para-arsonate. It was first used in the treatment of trypanosome infection.

The drug was first used as an antisyphilitic measure by Lorenz[12] in 1924. He divided his cases into what he called their respective clinical types before active treatment was instigated. He did not pick his cases, except to the extent that each represented the average type case which presented itself for treatment.

Before active treatment was started, the following data was obtained: A Wassermann test of the blood-serum was performed in a manner that permitted of quantitative reading. The Wassermann reaction with the spinal fluid was also performed by serial dilutions of from 0.2 to 1 c.c. A cell count of the fresh fluid was made. Globulin was estimated by the Ross-Jones and Noguchi butyric-acid tests, and the Lange colloidal-gold test was made with each fluid. With laboratory data and a complete neurologic examination, the cases were divided into the following clinical types: Paresis, atypical paresis, asymptomatic paresis, meningovascular syphilis, tabes, and taboparesis.

For a diagnosis of paresis, the following were necessary: Definite mental abnormality associated with a positive Wassermann of the blood and spinal fluid, a cell count of from 20 to 50 per c.mm., a positive globulin test, and a paretic type of "gold solution" curve. These serologic findings had to be present with some neurologic abnormality in the nature of pupillary changes, disturbances of reflexes, muscular incoördination, or other mental changes as grandiose ideas, euphoria, or other signs common to paresis.

The term "atypical paresis" was reserved for the cases presenting the clinical manifestations of paresis, but with negative blood Wassermann and atypical spinal-fluid findings.

Asymptomatic paresis was applied to those cases which showed the serologic and neurologic characteristics of paresis, but in which the mental picture was lacking.

Meningovascular types were, predominantly, cases that presented complaints of headaches and dizziness with many neurologic abnormalities usually better developed in paresis, but nevertheless distinctly present in this group. The spinal fluid is usually differentiated from the paretic type by a lesser degree of positiveness in the Wassermann test, more fluid being required to bring about the positive reaction.

Tabes and taboparesis present such typical pictures familiar to all; it is unnecessary to go into them here.

After classifying the groups as above described, active treatment was started. This consists of the weekly intravenous in-

jection for eight weeks of 2 to 3 gm. of tryparsamid, the drug being dissolved in 10 c.c. of sterile water, and filtered through a sterile filter-paper. Midway between the tryparsamid injections 32 to 65 mg. of mercury salicylate was given intramuscularly, 8 doses in all being given. This comprised one course of treatment.

The following report[12] of 185 cases collected from the literature will give a good idea as to the results to be expected from such therapeutic measures.

Paresis.—Report of 84 cases. These varied in their clinical picture from those sufficiently psychopathic to warrant institutional supervision, to others distinctly euphoric and delusional, with memory defects and other evidence of mental deterioration. The majority, however, were ambulatory and may have passed for normal, but on close examination showed changes in character, reduced capacity for work, changes in interests or lack of interest, etc. They all showed a completely positive serology before treatment with tryparsamid and mercury salicylate was started.

The clinical results of these cases are as follows: Thirty-seven cases, or 41 per cent., were mentally restored; 38 were distinctly improved; 9 remained unchanged; in 6 the mental manifestations progressed regardless of the treatment.

The effect on the serology was not so marked. The blood Wassermann became negative in 49 cases or 54 per cent.; was reduced in 17; remained stationary in 15, and became more positive in 3.

In 6 cases the spinal fluid became completely normal; in 36 a marked improvement was noted.

The 36 cases that were mentally restored received from 16 to 48 doses of tryparsamid and mercury salicylate. All cases were started with 0.3 gm. doses. In 2 cases the treatment was interrupted because of amblyopia, but subsequently tryparsamid was resumed, and no further eye symptoms were noted.

Atypical Paresis.—Six cases were so diagnosed, because from their clinical histories they would have been classed as paresis, but their negative blood Wassermann and atypical

spinal fluid forced them into this group. Of these, one made a remarkable recovery after 16 injections of tryparsamid. The other 5 cases showed some improvement in their mental condition.

Asymptomatic Paresis.—These showed the serologic findings of paresis with mental derangement. Neurologic symptoms were present in the nature of pupillary anomalies, disturbances of deep reflexes, tremors, and, frequently, speech defects. In these cases, the blood and spinal fluid were strongly positive with small amounts. In order to class these cases as asymptomatic paresis, the colloidal-gold curve must be of the paretic type.

As these cases are predominantly serologic conditions associated with physical signs which are slightly, if at all affected by any form of antiluetic treatment, the evidence therefore of therapeutic effect must be sought for in the serology.

In the treatment of 23 cases of asymptomatic paresis, the following results were obtained: In 19, the blood Wassermann became negative. Of these, the spinal fluid of one became negative after 16 injections of 3 gm. doses. In 6, the spinal fluid was very much improved. The cell count was reduced to within normal range; the globulin test became negative or slightly positive; the Wassermann either became entirely negative, or a positive reaction was obtained only when large amounts of fluid were used, where previously a positive reaction had been obtained with small amounts. The paretic type of gold curve disappeared, and in its place a reaction simulating that of meningovascular syphilis was obtained. Of the remaining 5 cases, 4 showed practically no improvement after 16 injections of tryparsamid had been given, and the disease seemed to be hastened in one.

Meningovascular Syphilis.—In this group subjective as well as objective symptoms are obtained, and in order for a case of this type to be classed as improved means a clinical improvement in subjective findings as well as an improvement in the serologic changes.

Twenty-nine cases were placed in this group. Of these, all but 6 had positive blood Wassermanns; of the 6 whose blood Wassermann was negative, the spinal fluid was positive. Of the

total number of cases, 19 (or 66 per cent.) showed complete recovery after from 20 to 40 injections of tryparsamid, extending over a period of from eight to twenty months, had been given. Seven were much improved, while 3 remained unchanged.

In 5 of the clinical recoveries the blood and spinal fluid both became completely negative. This would represent 17 per cent., in which perfect results were obtained. In 13 of the clinical recoveries, the fluid was markedly improved; in 7, favorably affected. The blood Wassermann became negative in 11, or practically 50 per cent., after 16 to 24 injections had been given.

One case came in complaining of severe headache, dizziness, and mental fatigue. He showed unequal pupils, and exaggerated deep reflexes. His serology was negative before treatment was started. During the three years previous to this patient's admission, he had received 20 injections of neo-arsphenamin and 40 injections of mercury. He was given 3 gm. doses of tryparsamid, but no mercury was used. After 8 injections he was symptom free.

Tabes and Taboparesis.—A total of 43 cases were classified and placed in this group; of these, 29 were tabetics. All had had active antiluetic treatment previously, without benefit. The chief complaint of most of these was severe crises characteristic of the preataxic stage of tabes. Ten cases were much relieved, had better muscular control, and showed marked improvement in general health. They were given from 32 to 40 3-gm. doses.

Sixteen of the 29 cases showed a positive blood before treatment; 10 of these became negative after 2 or 3 courses of treatment. Twenty-seven of the 29 showed a pathologic spinal fluid, but less marked than in paresis; in some the colloidal gold curve alone being positive or a weak globulin test. The Wassermann reaction was positive only with larger amounts of fluid, the cell count was not infrequently found to be normal. In 3 cases the spinal fluid became completely negative and in 16 a decided improvement was noted.

In 16 of the 29 tabetics, treatment was ineffective.

Summary.—From the foregoing discussion it has been shown, that 20 per cent. of paretics treated by the malaria-inoculation

method show complete remissions, with Sodaku 22 per cent. of complete remissions have been reported, while the tryparsamid-with-mercury-salicylate method yields 41 per cent. of clinical remissions. Relapsing fever does not offer results worthy of its consideration.

Conclusion.—1. Blood taken at any time during the course of malaria may be used for inoculation. It need not be taken during or immediately after a chill.

2. A strain of malaria may be passed from patient to patient indefinitely.

3. Some patients are immune to malaria inoculation.

4. Inoculation malaria is very sensitive to quinin.

5. Physical and mental improvement runs hand in hand, but the serology is only slightly affected.

6. Inoculation malaria becomes entirely asexual in type, and cannot be transmitted by the mosquito.

7. The malaria treatment is a distinct advance, but is not without danger. The death rate from its use being 10 per cent.

8. Sodaku may be used in more debilitated individuals than can malaria.

9. Sodaku can be maintained in experimental animals.

10. The death rate from the use of Sodaku is about 3 per cent.

11. Tryparsamid offers no disadvantages except amblyopia, which occurs in about 10 per cent. of patients thus treated, disappears without harmful effects, and returns in only 1 per cent.[13] on the subsequent use of the drug.

12. In the proper hospital surroundings, where an acute febrile reaction is desired, I think that Sodaku offers more advantages than does any of the fever-producing substances thus far used, but, for use in general practice, tryparsamid is by far the best drug to use.

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HYPERTROPHIC OSTEO-ARTHROPATHY

CLUBBING of the fingers and toes had been recognized as a clinical manifestation of intrathoracic disease from the earliest times, and, from the place of importance given this condition by Hippocrates, it is evident that the ancients were cognizant of the effects wrought by chronic pulmonary phthisis. Until 1889, when interest in hypertrophic, pulmonary osteo-arthropathy was revived by the investigations of Bamberger[1] and Marie,[2] this condition had rarely been discussed to any appreciable extent.

The definition of hypertrophic, pulmonary osteo-arthropathy as given by Carr,[3] is a disease of secondary nature occurring in the course of various chronic conditions, characterized clinically by enlargement of the extremities with clubbing of the fingers, and thickening at the joints, or about them, and, anatomically, by thickening of the soft parts, especially of the distal phalanges and proliferative processes of the periosteum, particularly at the lower ends of the bones. With the exception of the clubbing of the fingers and toes, and, rarely, by observation of thickening of the distal extremities of the long bones, the disease requires the use of the Roentgen-ray for its diagnosis. It is found as a secondary manifestation of chronic diseases of the heart and lungs, the most important of which are bronchiectasis, pulmonary tuberculosis, chronic empyema, and congenital heart lesions. Chronic jaundice, chronic alcoholism, pyloric obstruction, enterogenous cyanosis, pyelonephritis, dysentery, syphilis, purpura, malaria, and polycythemia with enlargement of the spleen are said to be the exciting factor in certain instances.

Norris[4] claims that clubbing of the fingers is often a valuable sign in subacute, bacterial endocarditis, bearing out the investi-

gations of Cotton[5] in this field. Teleky[6] classified the possible etiologic factors as follows:

1. Diseases characterized by purulent and gangrenous processes in the body, as pulmonary tuberculosis with cavitation, bronchiectasis, empyema, cystopyelonephritis, and dysentery.

2. Infectious diseases and chronic intoxications, as pneumonia, pleurisy, syphilis, and alcoholism.

3. Cardiac diseases, especially the congenital type.

4. Malignancies of the lung.

5. Diseases of the nervous system, as syringomyelia and neuritis. Nearly all the investigators of the present day question the possibility that nervous diseases are etiologic factors, and Hogler omits cardiac disease and adds hepatic cirrhoses, attributing unilateral clubbing to aneurysm of the aorta, or of its large branches, with pressure on the principal nerves to the affected extremity.

That clubbing of the fingers in pulmonary tuberculosis is of valuable diagnostic and prognostic significance has been discussed for many years. However, in an investigation of some 150 cases of advanced pulmonary tuberculosis at Charity Hospital during the past year, not more than 9 per cent. showed any evidence of clubbing of the fingers, the majority showing only signs of early clubbing, most of which were very slight, and were not in the least typical. The largest number showed a "parrot-beaking" effect of the finger- and toe-nails, with very slight or no signs of clubbing.

A comprehensive report of 8 cases was published by Pierre Marie[2] in 1890, describing in detail the changes in the long bones, and calling this condition hypertrophic, pulmonary osteo-arthropathy. According to Carr, this hypertrophic pulmonary osteo-arthropathy is a disease of two stages, the first of which often exists long before signs of the more advanced state are present. It can only be said to be secondary, for with our present knowledge we are unable to prove that it is primary. Bamberger[1] reported to the Medical Society of Vienna in 1899, 2 cases of bronchiectasis that showed wide-spread involvement of the wrists, ankles, and elbows, and tenderness over the patellæ and thighs. These cases

were regarded as a diffuse hypertrophy of the bones, the etiology of which is uncertain. Steinberg considers three types: (1) Pure clubbed fingers; (2) clubbed fingers with transitory periosteal deposits on the distal ends of the bones of the extremities (Bamberger's type), and (3) joint and bone changes of the severe type (Marie's type) A fourth type is added by Hogler, covering a case by Schlagenhaufer, in which there were typical periosteal deposits without clubbing.

Although we can cite with certainty the numerous diseases in which hypertrophic osteo-arthropathy exists as a secondary manifestation, we have yet to determine the true etiology and the mechanism of its production. There appear to be but two possibilities: (1) Sepsis, which is most often limited to the lung, giving us reason to believe that hypertrophic osteo-arthropathy is due to sepsis alone, and (2) passive congestion in the most dependent parts of the body. Braun considers it to be due to an endocrine disturbance, but this hypothesis does not find favor. Brooks,[7] quoting Zeigler, has pointed out that a continued peripheral hyperemia is produced by a compression of the lung capillaries in pneumonia, pleural and mediastinal disease. This appears to be the fundamental etiologic mechanism adhered to by practically all writers. According to Marie,[2] toxins are produced in a focus of infection, and these toxins are absorbed into the circulation and are carried through the body. Bamberger[1] has added the passive congestion theory. A fourth possibility to be considered is a combination of the passive congestion theory and the sepsis theory, viz., toxins eliminated from a focus of infection and carried in the blood act as capillary dilators. The capillaries of the distal portions of the extremities becoming dilated, and being already subjected to a greater hydrostatic pressure, are now chronically engorged. This hyperemia gives the extremity its cyanotic appearance, and later brings about a proliferation of the distal phalanges of the hands and feet. The capillaries supplying the phalangeal periosteum may be the first to become involved, with the resultant fibroblastic and osteoblastic stimulation, and the deposition of the typical layer of subperiosteal new bone. The digital pulp undergoes somewhat of an increase,

giving the fingers their typical drum-stick appearance. The base of the nail is widened, and this, according to Freytag, is due to a dilatation of the capillary loops in the nail-bed. Fowler and Godlee[11] claim it is due to overgrowth of the papillæ, which produces a marked prominence and mobility at the base of the nails. An added clinical manifestation which occasionally accompanies hypertrophic osteo-arthropathy is the production of a bulbous tip of the nose. This condition is undoubtedly brought about by the same mechanism which causes clubbing of the fingers. Kleinberg[8] reports a thickening of the tip of the nose, and, to a less marked degree, of the malar regions.

Changes in the nails have to do with their enlargement and their increased convexity. The beaking phenomenon of the nails occurs very early. Ebstein holds that Hippocrates noted the curvature of the nails and their association with chronic empyema.

Clubbing of the fingers may be due to an increase in the soft tissues only, or to associated bone-changes in the terminal phalanges, which may be more or less marked. Schlagenhaufer's case of typical periosteal deposits without clubbing is a curiosity, though, according to Landis,[4] clubbing of the fingers invariably occurs in secondary, hypertrophic osteo-arthropathy.

Cotton[5] has shown that the clubbing of the fingers produced in subacute, bacterial endocarditis is due to an embolic phenomenon in the terminal capillary loops of the distal ends of the fingers.

For the bone changes the Roentgen ray is required. The terminal phalanges of the hands and feet, at their distal ends, in well marked cases, show a widening and a thickening, and the shafts and bases of these phalanges are thicker and larger than normal. This enlargement is due largely to a thickening of the periosteum, and rarely to bone changes. The proliferation of the periosteum of the terminal phalanges is more likely to be found in associated, wide-spread osseous pathology. Locke[4] believes that careful Roentgen-ray study of the long bones will reveal alterations in many cases which clinically show clubbing only. On the basis of radiologic studies, Kessel[10] has shown that bone

changes occur more commonly than is ordinarily supposed in simple clubbed fingers. Kleinberg[8] writes that many men of wide experience have told him that they have never seen a case of hypertrophic osteo-arthropathy.

The essential, pathologic feature of the bone disease consists of a deposit of subperiosteal, new bone, usually manifesting itself at the distal ends of the diaphyses of the long bones of the arms and legs, and later involving the other bones of the skeleton. Radiologic examination will show this deposition of new bone along the shafts of all the long bones, which varies in thickness from a line to 3 mm. The carpal and tarsal groups, the clavicles, ribs and vertebræ, and usually the scapulæ, are not involved. The pelvis and the cranial bones have occasionally been reported as being subject to these changes, but it is doubted whether they were true cases of hypertrophic osteo-arthropathy. The thickening of the ends of the bones, especially at the lower ends, is characteristic, though the proliferations are not confined to these localities. Kauffmann says that at times, throughout their entire length, the bones of the arms and legs may be covered with flat periosteal deposits. Many writers call this typical periosteal pathology by the term "ossifying periostitis." Hogler does not consider this an inflammation, but calls it hyperplastic, and claims that it has nothing to do with the bone, but with the periosteal deposits alone. Some writers agree that the joints themselves participate in the morbid process, but this has never been generally accepted.

In long standing cases, the periosteum of all the bones may be involved. The normal tapering of the forearms and lower legs is completely lost, the ends of the bones and the periarticular structures may be involved to the extent of causing great pain and difficulty of movement. The lesions are usually more extensive in the lower than in the upper limbs and this may be due to venous stasis. Later, there may be great swelling of the limbs with no pain. The surface of the tibia may become very irregular, and the cortex may be very greatly thickened.

Upon careful observation, the earliest manifestations of these secondary changes have been noted as a loss of the normal

wrinkling of the fingers just proximal to the base of the nail, and an evident tenseness and paleness replacing the normal loose and vascular skin. This, in all probability, is due to a deposition of subperiosteal, new bone in the base of the distal phalanx, and the smooth, whiter appearance due to pressure exerted upon the skin by the subcutaneous tissues. Later, there is a broadening of the base of the nail, with an increase in the convexity in both diameters, due to the dermal papillary overgrowth of Fowler and Godlee.[11] The Roentgen ray, at this time, shows a deposition of subperiosteal, new bone along the shaft of the metacarpal and metatarsal bones, the fifth being the one commonly first affected. There may, or may not, be a true clubbing of the fingers at this time. The phalangeal bone changes take from three months to a year to become evident, though the clubbing is usually present before there is any evidence of the bony change. The two proximal phalanges become thicker, their heads and bases becoming larger. Following this, the long bones are gradually involved, at their distal ends and along their shafts. In many cases examined by Roentgen-ray, the new, subperiosteal bone-formation appeared along the shafts of the fifth metacarpal or metatarsal bones. However, in cases of marked and long-standing chronic diseases, in which definite clubbing of the fingers exists, the Roentgen ray may show no deposition of the subperiosteal, new bone in any of the skeletal system. Again, in cases of marked clubbing of the fingers, there may be no change in the phalanges, but distinct evidence of subperiosteal new-bone formation along the shafts of some of the long bones. In 3 recent cases in which clubbing of the fingers was well marked, no cardiac or pulmonary condition other than the normal could be determined either by usual clinical or Roentgen-ray methods.

CASE REPORTS

Case I.—B. W., white, male, twenty-five years old, was admitted to Charity Hospital in October, 1926, with a complaint of diarrhea, which had persisted for about six months. The patient had a history of having seven to ten stools during the day, and from four to six during the night. He said that his father and

brother had died with a severe diarrhea. The physical examination revealed a well developed, and fairly well nourished individual, weighing about 150 pounds, and appearing somewhat anemic. There was some tenderness and rigidity in the right hypochondrium. Proctoscopic examination showed typical amebic ulcers of the rectum. No motile amebæ could be found,

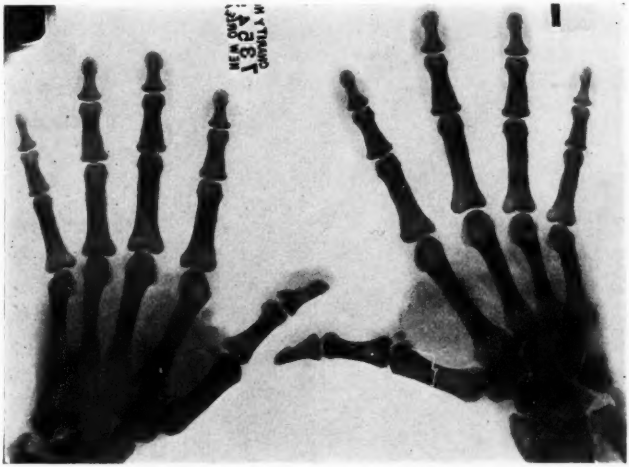

Fig. 202.—Skiagraph of hands of Case I showing moderate enlargement of the distal phalanges, but well-defined, subperiosteal ossification along the shaft of the fifth metacarpal bone, and to some extent also along the shafts of the other metacarpals and thickening of the proximal phalanges.

but many of the typical cystic forms were noted. Examination of the blood revealed a secondary anemia. Clubbing of the fingers was fairly well developed, and Roentgen-ray examination showed periosteal deposits in the terminal phalanges and the metacarpals, especially along the shaft of the fifth metacarpal.

Case II.—A. I., colored, male, thirty-seven years of age, a farmer by occupation, was admitted to Charity Hospital in December, 1926, complaining of weakness and loss of weight. A history of continued, yellowish discoloration of the sclera, which had persisted as long as the patient could remember, was ob-

tained. He claimed that he had had several such attacks, and that occasionally he had noticed a slight pain in the right hypochondriac region. There had been no other pains, nor vomiting. Physical examination showed slightly jaundiced scleræ, soft systolic murmur at the apex of the heart, and a palpable spleen. The Wassermann reaction was negative. The number of ery-

Fig. 203.—Skiagraph of the hands of Case II showing generalized enlargement of the distal phalanges, with marked clubbing of the fingers. The hypertrophic osteo-arthropathy involves the terminal phalanges. There is definite ossifying periostitis of the shafts of the metacarpals and a thickening of the ends of the proximal phalanges.

throcytes was 1,525,000, the hemoglobin 50 per cent., and the leukocytes 7200. After remaining in the medical ward for three days, the patient deserted, but not before a Roentgen-ray examination was made of his hands. The skiagraph showed definite deposition of subperiosteal, new bone in the terminal phalanges and in the first phalanges, also in the shafts of the metacarpals.

Case III.—J. B., white, male, twenty-seven years of age, a bartender by occupation, was admitted to Hotel Dieu with a submental abscess of four months' duration. The abscess had begun as a localized area of swelling and redness, which was opened by his physician as soon as fluctuation was noticed. The lesion seemed to be superficial, but in the past four months it required incising several times. At this time, an incision was made, and the mandible was curetted. Clinically, the patient was physically sound, but the skin was a yellowish-olive tint, and there was definite clubbing of the fingers and toes. No evidence of pulmonary tuberculosis could be obtained.

DIFFERENTIAL DIAGNOSIS

Acromegaly should be differentiated from hypertrophic osteo-arthropathy. It is a disease in which the bones are enlarged, but the typical periosteal proliferations of hypertrophic osteo-arthropathy are absent. The enlargement of the lower jaw is characteristic, and joint changes are not a part of acromegaly. There is absence of a history of chronic disease of the respiratory tract, or of congenital heart-lesions. The hands and feet in acromegaly are not deformed, but are merely enlarged.

With clubbed fingers, one must not confuse Heberden's nodes, which are small exostoses at the proximal ends of the terminal phalanges on the dorsal side, pea-sized, and may be painful. They are associated with arthritis deformans.

There is no known treatment for the condition. Occasionally, by treating the primary disease, some relief may result.

SUMMARY

1. Clubbing of the fingers is often of great clinical value in the diagnosis of chronic, pulmonary, and congenital cardiac lesions, and leads us to suspect the presence of long-standing, low-grade infections.

2. The existence of two classes, simple clubbing of the fingers, and clubbing with associated bone changes.

3. The essential pathologic feature is a deposition of sub-

periosteal, new bone in the terminal phalanges, and along the shafts of the long bones.

4. The cause is essentially sepsis, combined with a capillary dilatation, with fibroblastic and osteoblastic stimulation in the distal ends of the long bones.

5. Hypertrophic osteo-arthropathy may be present in the absence of demonstrable pathologic conditions.

6. It may be confused with acromegaly, as was one of Marie's cases, or with Heberden's nodes of arthritis deformans.

7. There is no known remedy for the condition, except treatment of the primary disease, if diagnosed.

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THE EFFECTS OF ANTITOXIN ON THE LEUKOCYTOSIS IN DIPHTHERIA

INASMUCH as there has been a relatively small amount of work done on the reactionary changes brought about by the introduction of various antitoxins and vaccines into the body, the author has attempted to observe the changes, if any, in the blood by the administration of antitoxin in diphtheria. The material for this paper has been taken from the blood findings in 33 selected cases of diphtheria. While this is a rather small number of cases, I believe the fact will be appreciated that all of the cases admitted to Charity Hospital with a diagnosis of diphtheria could not be used in this observation. The following cases were of no use to us: (1) Those cases in which Klebs-Löffler bacilli could not be obtained through throat or nasal cultures; (2) those in which no control blood-count was obtainable before the antitoxin was given; (3) those in which some other infectious disease, as pneumonia, developed during the observations, thus making the blood findings inaccurate; (4) those which ended in death before the observations were far enough under headway.

Of these 33 cases, there were 8 of the tonsillar type, 6 of the laryngeal type, 15 of the tonsillar-laryngeal type, 2 of the tonsillar-laryngeal-nasal type, and 2 of the tonsillar-nasal type.

The purpose of this work was to determine the changes in both the total leukocyte count and in the differential count caused by the administration of diphtheria antitoxin. To do this it was necessary to obtain a total leukocyte and differential count just before the administration of the antitoxin. Where it was possible, counts were made within one hour of the giving of the serum

to determine at what time the total leukocyte count was affected by the antitoxin. Subsequent counts were made every two, three, or four hours following, in order to observe the time at which the action of the serum was at its height. Differential counts were made daily to determine the effects of the serum on the neutrophils, and to note a possible eosinophilia due to a serum reaction.

In order to lessen the possibility of error in the work, the leukocyte counts were made with pipets and counting chambers which had been standardized by the United States Bureau of Standards, or with those which had been closely checked by such instruments.

Turning now to the observations made in this work, from Fig. 204 it is seen, from the changes in the leukocyte count, that either a decrease or an increase took place in most of the cases during the first or second hour after the antitoxin had been administered. The time it took for the total count to become normal varied to a great extent, and in some instances three or four days elapsed before this occurred. Concerning the action of the antitoxin on the total leukocyte count, as seen in Fig. 205, this group of cases can be divided into four classes as follows:

Class I.—Those cases in which there was a definite leukocytosis, and the antitoxin caused a further increase in the total count. Fourteen cases fell into this class. This was 42 per cent. of the total series.

Class II.—Those cases in which there was a slight leukocytosis, and the antitoxin caused an increase in the total count. Four cases came in this group, or 12 per cent. of the series.

Class III.—Those cases in which there was a definite leukocytosis, and the antitoxin caused a decrease in the total count. Thirteen cases, or 40 per cent. of the total number, fell into this class.

Class IV.—Those cases in which there was a leukopenia, and the antitoxin caused an increase in the total count. Only 2 of the 33 cases came in this group, that is 6 per cent.

Regardless of the total count before the administration of the

antitoxin, 20 of the 33 cases showed an increase in the total count after the giving of the serum.

Referring to Fig. 205, which shows the differential count of the cases, it will be noted that no constant rules were followed in the reaction of the different forms of leukocytes. In 30 of the cases where the differential count was taken twenty-four to forty-eight hours after the antitoxin was given, 10 of the cases

Case Number	Count before Serum.	Count 1 hr. after serum	Count 2 hrs after serum	Count 4 hrs after serum	Count 6 hrs after serum	Count 12 hrs after serum	Count 20 hrs after serum	Count 40 hrs after serum	Count 56 hrs after serum	Units of antitoxin given	Age of patient
1	18,250		20,000	18,500	14,400	12,250				30,000	5 mos
2	32,750		30,000	31,250		25,500	18,000			10,000	8 yrs
3	48,500	37,500	36,200	36,400	33,000		34,200	21,000	16,500	10,000	7 yrs
4	42,000		38,300	37,250	32,250	32,250	28,250	20,000	16,250	30,000	2 yrs
5	17,250	18,100		18,600	20,000	25,200	18,000	8,250		10,000	14 yrs
6	17,750			14,200	12,500		10,100			10,000	
7	26,250		26,000	22,200	19,200	12,250	21,300			30,000	3 yrs
8	10,000	10,200	11,700	13,500	13,000	12,000	11,400	10,500	9,750		
9	26,200		24,750	18,200	17,700		20,250	26,200		30,000	2 yrs
10	3,500	3,400	3,100	3,500	3,500	4,300	5,700	9,000	12,750	10,000	26 yrs
11	43,600	34,200		31,500	24,200	20,000	24,000	12,250		30,000	6 yrs
12	16,300		16,250	15,750	13,250		16,000		8,750	10,000	3 yrs
13	10,750		11,000	10,300	10,250	9,250	" 8,500		9,250	10,000	10 yrs
14	10,300		12,500	17,300	14,000	17,000	" 13,500	8,250		10,000	11 yrs
15	24,900	28,500		23,000	23,400	11,500				60,000	4 yrs
16	6,750		8,000	11,000	13,200	13,250				10,000	6 yrs
17	12,250		7,000		18,150	14,200	16,250	13,500	10,250	30,000	2 yrs
18	23,750	22,000	24,000	25,000	21,500		17,000			30,000	4 yrs
19	12,000		12,250	14,750	40,000		14 17,000			40,000	5 yrs
20	29,500	32,300	34,000	39,500						60,000	3 yrs
21	32,200		24,750	25,000		18,200	13,500		9,750	60,000	4 yrs
22	40,500	35,750		29,000	25,200		20,750			70,000	11 yrs
23	9,500	11,500	15,500	14,000		18,750				60,000	3 yrs
24	28,250		33,300				14 14,500			60,000	2 yrs
25	13,000		17,250		16,900		14 12,000			60,000	4 yrs
26	26,000		30,250	37,750		22,300	17,500			60,000	5 yrs
27	22,250	26,200		25,200	26,000		24,000	15,000		60,000	3 yrs
28	33,500	25,000		17,250						40,000	5 yrs
29	14,500		23,500	22,250		13,600	12,600			60,000	2 yrs
30	33,750	34,800		35,250		27,900	18,250			50,000	7 yrs
31	20,000		22,300		20,200		15,750			20,000	10 yrs
32	14,350	22,000	24,400	26,250		14 18,800	14 15,100			10,000	8 yrs
33	16,250	18,000	23,800	30,750	34,000	24,500		18,000		60,000	3 yrs

Fig. 204.—Over some of the figures will be seen a number which designates that the count was made that number of hours after the serum had been given, rather than the number at the top of the column.

revealed an increase in the percentage of neutrophils, while 18 cases showed a decrease in the neutrophils. Another interesting point in this respect was that 4 cases, *i. e.* cases No. 3, 5, 10, and 32, revealed a definite eosinophilia which in two of the cases went as high as 12 and 13 per cent. These 4 cases received only 10,000 units each of antitoxin, while the others, which received massive doses as 40,000 or 60,000 units, showed no indication of an eosinophilia. This appears to be rather inconsistent with the

results we would expect, that is if we attribute the eosinophilia to a serum reaction.

Another feature of the differential count was a point brought out by Ewing in a work similar to this, namely the staining power of the leukocytes. My findings in this respect were as follows: The various leukocytes, especially the neutrophils, before the

	Differential count before serum.						Differential count 4-6 hrs after serum						Differential count 24-48 hrs after serum					
Case	N	S	L	E	B		N	S	L	E	B		N	S	L	E	B	
1	70	24	6				72	25	3				79	11	10			
2	91	5	4				90	5	5				84	8	5	2	1	
3	82	12	6				80	15	5				76	11	4	9		
4	89	9	2				85	13	2				74	7	12	2		
5	91	5	4				90	8	2				74	3	4	12		
6	75	12	12	1									73	6	9	2		
7	88	7	5				74	13	6	2			73	17	9	1		
8	64	13	19	3	1		80	10	10				74	10	15	1		
9	85	3	12				80	11	9				76	18	3	2	1	
10	73	13	12				74	15	11				70	16	8	6		
11	69	23	8				74	17	4				72	19	8	1		
12	68	10	21	1									60	20	20			
13	37	43	19	1			64	25	11				58	39	2	1		
14	57	37	6				25	33	12									
15	90	4	6				12	3	5									
16	65	10	19	1	2		72	16	8	3	1		70	19	7	2	1	
17	74	18	8				86	5	9				80	13	16	1		
18	70	17	13				87	6	7				75	12	13			
19	30	23	47				37	19	44				41	32	26	1		
20	73	3	24				86	7	6		1							
21	89	2	9				84	9	7				90	5	5			
22	89	9	2				67	11	2				60	32	7	1		
23	41	41	18				30	57	13				74	19	7			
24	74	8	13				74	9	12	4	1		68	18	12	2	1	
25	78	14	8										60	35	4		1	
26	96	3	1				90	5	5				76	15	8		1	
27	70	25	5										62	27	9	2		
28	82	10	8				79	14	7									
29	70	23	3				71	21	3	5			68	25	7	2	1	
30	86	8	6				81	11	8				77	15	7		1	
31	75	16	9										70	21	8	1		
32	76	16	8				70	21	9				52	10	25	13		
33	70	16	14				74	17	9				70	19	10	1		

Fig. 205.—Differential blood counts before and after antitoxin.

administration of the antitoxin in many cases took a rather faint stain; furthermore the cytoplasm of the neutrophils appeared to be of a more granular nature than would be found in the normal cell. After the serum had been given the cells seemed to take more of the stain, and when this occurred the granular appearance of the cytoplasm was not as marked as before. While these findings were not observed in every case, I do not believe that the

variation in the staining power of the leukocytes can be attributed altogether to the technic in the staining of these blood-films.

DISCUSSION

Gabritschewsky,[1] in 1894, first called attention of hyperleukocytosis occurring in diphtheria, and proved by experiments on animals that this condition was due to the toxins of diphtheria. Schlesinger,[2] by inoculating guinea-pigs, has drawn the same conclusions. He states that occasionally the cells were increased two to four times the normal number, and that the increase was chiefly in the polymorphonuclear elements. In the fatal cases, the condition was continued to the end, and differed in that respect from the condition caused by other infectious diseases. Lovett Morse[3] states that hyperleukocytosis probably begins with the disease, and is most marked at the height of the disease, after which it declines. Ewing has made some interesting observations on the effects of antitoxin on the hyperleukocytosis which has already been noted as regularly occurring in diphtheria. In Ewing's 18 cases there was a diminution in the total leukocytic count in 15 cases after the injection of the antitoxin. This diminution affects chiefly the faintly staining mononuclear and the polymorphonuclear cells. He also found that the antitoxin affected the staining power of the leukocytes, and in five children in which this did not take place death occurred. Ewing believes that the hypoleukocytosis is due to the antitoxin, and when it does not occur a fatal outcome is to be expected. Schlesinger has confirmed these results.

As stated above, 20 out of the 33 cases of this series showed an increase in the total leukocyte count after the administration of the serum. These results are not in keeping with the findings obtained by Ewing, for the great majority of his cases showed a decrease in the total leukocyte count. It would seem plausible, I believe, to expect an increase in the total white-cell count after the giving of the antitoxin, if for no other reason than the fact that a foreign protein here in the form of horse-serum had been introduced into the body. Furthermore, the temperature curve after the giving of the serum was rather characteristic. In 24 of

the cases, that is, 72 per cent. of the series, there was an increase in the temperature, usually a rise of 2 or 3 degrees. This increase took place during the first, second, or third hour after the administration of the antitoxin. In only 5 cases was there a fall in the temperature curve. In 4 cases no changes were noted in this respect. This feature can probably be explained just as the increase in the leukocyte count, namely, that a foreign protein had been put into the circulation. The rise in the temperature as mentioned above was, however, only a transient affair, for in the majority of the cases the rise was in the course of four or six hours followed by a gradual decline.

CONCLUSIONS

I. The change in the total leukocyte count was noted within an hour or two after the serum had been given.

II. That 6 out of every 10 cases showed an increase in the total leukocyte count after the serum had been administered.

III. That the size of the dose did not materially affect the total white-cell count or the differential count.

IV. That the staining power of the leukocytes, especially the neutrophils, were affected by the antitoxin in many of the cases.

V. That a marked eosinophilia was found in four of the observations.

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CLINIC OF DR. D. R. WOMACK

CHARITY HOSPITAL

MENINGOCOCCAL MENINGITIS TREATED WITH CISTERNAL PUNCTURE

MRS. E. B., white, twenty-four years old, housewife, was admitted to Charity Hospital September 18, 1926 and discharged October 9, 1926.

Chief Complaint.—Repeated chills. Diffuse headache.

Present Illness.—Seven weeks ago (Saturday, August 21, 1926) the patient was awakened at 4 A. M. with a chill. She went back to sleep, and got up that morning feeling well enough to go about her work as usual. Sunday she had another chill of ten minutes' duration, which was relieved with brandy. She played cards Sunday afternoon, and continued to feel well Monday and Tuesday. Wednesday morning she had a sudden attack of pains in her head, which increased in severity until the patient became comatose, in which condition she was taken to Mercy Hospital at 11 A. M. (August 24th). She regained consciousness Thursday afternoon at 4 P. M.

The patient remained in Mercy Hospital three weeks with headache and stiffness of the neck muscles, during which time her condition was not diagnosed, and her attending physician merely said she was "all right." As she did not improve, the first doctor was dismissed and a second called in, who did a lumbar puncture on September 14th, and found meningococci in the spinal fluid. She was then given an unknown amount of antimeningococcic serum in the vein, and an unknown amount in the muscle and sent to Charity Hospital.

The patient felt well and strong up to the time of her initial chill, and also in the intervals between chills.

Her appetite is good. The bowels are constipated. She urinates three or four times a day and none at night; there is no burning, pain, or discomfort attending the act. No vaginal discharge.

Menstrual History.—Menstruation began at fourteen years. It was regular every twenty-eight days, and of five or six days' duration. The flow was normal in amount and attended by no pain. The last period was sometime in March, 1926.

Marital History.—Patient has been married for two years. Has one child, fifteen months old; a normal delivery followed by a normal puerperium. No miscarriages. Patient is six or six and a half months pregnant.

Past History.—The patient has had no operations or accidents and denies all diseases.

Family History.—Father is living and well at the age of fifty-nine. Mother is living and well at the age of forty-eight. Two sisters are living and well. Family history is negative for tuberculosis, cancer, hemophilia, syphilis, and nervous disorders.

Social History.—Patient does general housework. Lives in a well ventilated home under good sanitary conditions. She is a hearty eater, and drinks one cup of coffee a day. She does not drink alcohol.

Physical examination reveals a well developed and well nourished white female lying comfortably in bed and sleeping most of the time. She is about 5 feet 6 inches in height, and weighs about 140 pounds.

Head.—Skull is normal in size and contour. Pupils are equal, dilated, and react to light and accommodation. The nose is negative, and no discharge is present. Ears are negative with no discharge. The mouth is anemic, the tonsils are not enlarged, and the teeth are in good condition except for one or two which are decayed.

Neck.—There is no adenopathy, and the thyroid is not enlarged. The neck is stiff anteroposteriorly. Lateral stiffness is not so marked.

Thorax is bilaterally symmetrical of the hypo-asthenic type. The heart and lung findings are negative.

Abdomen is negative except for a rounded tumor extending from the symphysis to the umbilicus. Fetal heart-sounds are heard. A *tache cérébrale* is present. There are no areas of disturbed sensibility, and the abdominal reflexes are normal except increased on the right.

Extremities.—The lymph-glands are not palpable. The abdominal, patellar, and tricep reflexes are slightly increased on the right side. Kernig's sign is positive. There are no pathologic reflexes. There is some rigidity of the spine.

Progress Notes:

September 18th

4 P. M.—Spinal puncture: 30 c.c. of serum given intraspinally and 30 c.c. intravenously.

11 P. M.—Spinal puncture: 25 c.c. of cloudy fluid under moderate pressure obtained; 18 c.c. New York City Board of Health antimeningococcal serum injected by gravity.

The spinal fluid showed:

Cell count	1750
Globulin	4 +
Wassermann	Negative

September 20th

Spinal puncture: 32 c.c. of moderately cloudy fluid under high pressure obtained; 27 c.c. of antimeningococcal serum injected by gravity.

The spinal fluid showed:

Cell count	2200 with some clots
Globulin	4 +

Pus-cells and Gram-negative intra- and extracellular diplococci, morphologically meningococci.

No growth on culture.

Urinalysis negative.

September 21st

Cisternal puncture and 25 c.c. of "cocoanut milk" fluid under normal pressure obtained; 20 c.c. of serum was injected. The patient showed signs of shock.

The spinal fluid showed:

Cell count..... 1830
No growth on culture.
Smear was negative for meningococci.

Blood Wassermann was negative.
Blood-culture showed no growth.

September 23d

Cisternal puncture: 40 c.c. of "cocoanut milk" fluid obtained; 35 c.c. of serum injected.

Spinal puncture: 10 c.c. of cloudy fluid removed and 18 c.c. of serum injected.

Patient had morphia, gr. $\frac{1}{4}$, an hour before the puncture, and another similar dose immediately preceding the puncture. No signs of shock were evident this time.

The spinal fluid showed:

Cell count..... 1780 with some clots
No growth on culture.

September 24th

Spinal puncture: 35 c.c. fluid removed; 18 c.c. serum injected.
The spinal fluid showed:

Cell count..... 2500
Sugar..... 55 mg. per 100 c.c.
No meningococci.

Nasopharyngeal cultures negative for meningococci.

September 25th

Spinal puncture: 28 c.c. of "cocoanut milk" fluid, under 16 to 18 mm. pressure, obtained; 18 c.c. serum injected.

The spinal fluid showed:

Cell count..... 3000
No meningococci.

September 26th

Cisternal puncture at 11.30 A. M.—35 c.c. of "cocoanut milk" fluid, under 16 mm. pressure, obtained; 17 c.c. serum njected.

The cisternal fluid showed:

Cell count..... 2200
1 lymphocyte to 400 neutrophils.
Some flocculi.
No meningococci.

Patient had projectile vomiting at 2 and 5 P. M. Slight serum rash on face and chest. Slight internal strabismus of left eye.

Spinal puncture: 25 c.c. fluid removed.

The spinal fluid showed:

Cell count..... 890
No meningococci.
Much clearer.

September 27th

Spinal puncture: 30 c.c. of cloudy fluid obtained. 18 c.c. serum injected.

The spinal fluid showed:

Cell count..... 1950
No meningococci.
No growth on culture.

September 28th

Spinal puncture: 35 c.c. of fluid obtained; 18 c.c. serum injected.

The spinal fluid showed:

Cell count..... 348
Colloidal gold..... 1000000000
Globulin..... 4 +

Serum rash better.

September 29th

Spinal puncture: 35 c.c. of slightly turbid fluid obtained; 5 c.c. of serum injected.

The spinal fluid showed:

Cell count..... 348

September 30th

Spinal puncture: 15 c.c. of slightly turbid fluid, under no increase of pressure, obtained; 5 c.c. of serum injected.

The spinal fluid showed:

Cell count	255
Sugar	55 mg. per 100 c.c.

Urinalysis negative.

October 4th

Spinal puncture: 20 c.c. of hazy fluid obtained; 8 c.c. of serum injected.

The spinal fluid showed:

Cell count	77
Globulin	3 +
Wassermann	Negative

Smear negative for meningococci.

The blood showed:

October 5th

Total white blood-cells	16,250
	Per cent.
Small lymphocytes	10
Large lymphocytes	2
Neutrophils	86
Eosinophils	0
Basophils	2
Total red blood-corpuscles	4,090,000.
Hemoglobin	85 per cent.

October 7th

The blood showed:

Total white blood-cells	10,600
	Per cent.
Small lymphocytes	10
Large lymphocytes	4
Neutrophils	86
Eosinophils	0
Basophils	0

Summary:

	Cubic centimeters.
Number of spinal punctures	12
Total amount of spinal fluid removed thus	320
Average amount of spinal fluid removed each period	26.6
Total amount of serum injected in spine	183
Average amount of serum at each spinal puncture	15.3
Number of cisternal punctures	3
Total amount of fluid removed thus	82
Average amount of fluid per puncture	27.6
Total amount of serum injected cisternally	90
Average amount of serum per cisternal puncture	30

Patient also received an unknown amount of serum intravenously and also intramuscularly on September 14th, and 30 c.c. of serum intravenously on September 18th.

Diagnosis in this case was not made until the first lumbar puncture was performed on September 14th. The only positive diagnosis is made by examination of the spinal fluid. This case should have been diagnosed sooner, as the patient was sick three weeks before a lumbar puncture was done.

Differential Diagnosis.—The only method of differentiating tuberculous, pneumococcic, influenzal, other purulent meningitides, meningismus, encephalitis lethargica, and acute anterior poliomyelitis is by examination of the spinal fluid. The types of spinal fluid encountered in each of these diseases will not be discussed here.

Rarer conditions which might be mistaken for meningitis are: Sunstroke, tetanus, intoxications, influenza, rheumatism, typhus fever, meningeal hemorrhage, and others.

Edward James[1] reports a case of meningococcal meningitis diagnosed as typhoid fever until a lumbar puncture was done on the ninth day. The onset was with generalized pains and abdominal discomfort. The Kernig sign was not positive until the ninth day, and a purpuric eruption did not show until the tenth day.

Complications and Sequelæ.—Relapses are rare, and are not seen after a few months have passed. Second attacks are not recorded.

Neal[2] says 82 per cent. make a complete recovery. The other 18 per cent. show sequelæ and these are often of a serious nature. These sequelæ develop, as a rule, during the acute stages of the disease, and are the direct and immediate result of the inflammatory process. This is in marked contrast to the sequelæ of epidemic encephalitis, which develops months or even years after the acute process has subsided.

Neal[2] further states that "the most important and frequent of the sequelæ is deafness. This is usually bilateral, complete, and permanent. Defects of vision are of rarer occurrence." Blindness is usually unilateral.

Other sequelæ are: Internal hydrocephalus, arthritis, conjunctivitis, epididymitis, iridocyclitis (seen in the French cases, and also those recorded by Neal), bed-sores and serum rashes.

It seems blindness (usually unilateral) is most likely to develop in infants, and deafness (bilateral, and complete, as a rule) in adults.

There is a wide-spread impression that epidemic meningitis is liable to be followed by defective mental development. Neal[2] says "our experience does not bear this out" and Gregory[3] reports a case nine years after the attack of meningitis which was treated with frequent ventricular punctures, and which showed no mental impairment.

As a sequela of treatment, Metzger[4] reports a case of paralysis of an eye muscle following a cisternal puncture.

Pregnancy is sometimes a complication, as in this case, and it is the rule that the infection brings about abortion.

Prognosis is much better since the introduction of serum treatment, which roughly[21] reduces the mortality from 55 or 70 per cent. to 25 or 30 per cent.

Osler[5] gives the following as the mortality rate when using the serum:

> 18.1 per cent. die when serum is given during first three days
> 27.2 per cent. die when serum is given fourth to seventh days
> 36.5 per cent. die when serum is given after the seventh day

hence early diagnosis and early administration of serum has a marked effect on the prognosis.

Of 17 cases of meningococcal meningitis at Charity Hospital[6] last year, 15 died and 2 were stationary (living at time of report). None were treated with cisternal puncture.

Treatment may be discussed under the heads of prophylaxis and active treatment. Very little will be said of the former. It might be mentioned, however, that overcrowding should be avoided, and carriers traced down by examination of nasopharyngeal cultures.

Many authors[7, 8] report very favorable results from the use of meningococcal emulsion containing 4,000,000,000 of the bacteria

per cubic centimeter given in three doses of 0.5, 1, and 1 each at eight-day intervals. This measure has checked several epidemics, it is stated. The use of vaccines is of value only in epidemics, however.

The active treatment may be divided into general and specific treatment.

The general treatment[9] includes isolation, with avoidance of all external stimuli. The patient was kept in a quiet room, which was darkened. The disease is a reportable one, and the public health office should be notified. The diet should be especially liberal, as there is a marked tendency to rapid wasting in this disease. The patient should be kept quiet with bromids and hypnotics if possible, and, morphia, if these measures fail. The bowels should receive proper care, and bed-sores should be prevented by the use of alcohol, powders, and mechanical means.

There is quite a difference of opinion regarding the serum treatment, both as to the method and amount of serum to be used. This patient received serum by both lumbar and cisternal punctures, as indicated in the progress notes.

Sophian[10] says, clinically, the serum diffuses into the ventricle after lumbar puncture, while agreeing that this is not so experimentally. He gives the serum by lumbar puncture, and judges the amount by the blood-pressure. He always stops the injection if the blood-pressure falls 20 mm.

Lewkowicz[11] says as long as the canal is clear a 10 per cent. concentration of the serum in the ventricles may be obtained. He agrees the ventricles are the chief focus of invasion, and if the spinal fluid by lumbar puncture is of low standard the ventricles must be punctured.

Some[12, 13] advocate spinal puncture, and the injection of 50 to 100 c.c. of air. The pelvis is then raised, and serum injected gradually by withdrawing 10 to 20 c.c. of air. The mortality is 25 per cent. with this method.

Herrick[14] maintains positive blood-cultures are observed in 45 per cent. of cases, and that a septicemia is very common in meningitis. He treats these cases with an average of at least 100 c.c. of serum in the vein every six, twelve, or twenty-four

hours depending on the severity of the case. The incidence of meningococcemia given by other authors is 25 per cent.

Herrick[15] states in another reference that during the premeningitic stage from 200 to 600 c.c. of serum should be given in the vein at the rate of 1 c.c. per minute for the first 15 c.c. and then more rapidly for the remainder. In the meningitic stage he gives 20 to 30 c.c. doses in the lumbar spine, and says ventricular puncture is a last resort in desperate cases.

Bruce and Flexner[16] seem to support Herrick in the importance of intravenous serum therapy by a case reported, in which no improvement was noted after lumbar and then cisternal puncture, which rapidly improved and recovered after the injection of 40 c.c. of serum in the vein. They explain the case as having an external focus of infection in the circulatory system which was not reached by spinal therapy, but which was reached by the intravenous route. They had a marked and severe reaction from the intravenous injection, and adrenalin and artificial respiration were required to revive the patient.

Discussion.—This case presents nothing unusual in its symptomatology, but the treatment is something new at Charity Hospital.

The sudden onset with a chill, followed by a period of seeming well-being, is a characteristic mode of onset for meningococcal meningitis. Next, we see coma and intense headache, which are among the initial symptoms of meningeal involvement. The phenomenon of onset may be easily explained, if we accept Herrick's theory concerning the high incidence of meningococcemia (45 per cent.) preceding the meningeal involvement—perhaps the initial fever and chill at onset are evidences of blood-stream invasion, and mark the premeningitic stage of the disease, then four days later the meningeal involvement manifests itself with headache, muscle stiffness, etc.

Such a high incidence of meningococcemia is disputed by most authorities, however, as they place the occurrence of positive blood-cultures at 25 per cent. This case showed a negative blood-culture on September 22d (one month after onset), but no blood-culture was made early in the case, so we should expect

the premeningitic stage to have passed by the time the culture was made. Nasopharyngeal cultures were negative on September 24th, which would show no local foci in the nasopharynx.

This case presented a slight serum-rash, but none of the characteristic purpuric spots of meningitis. This characteristic rash of meningitis is due to cutaneous emboli of meningococci, which can be cultivated from them, and it appears on the first or second day of the disease as a rule. Various figures as to the occurrence of the rash are given; one authority[17] says it occurs in 6 to 60 per cent. of cases—quite a large variation. The rash is rare in sporadic cases, common in septicemic cases, and constant in fulminating cases.

This patient presented the usual eye symptoms of papilloedema, internal strabismus, photophobia, nystagmus, and dilated pupils.

Her neck muscles were so stiff she could be raised in bed like a statue by lifting on the occiput.

The patient had no emesis at the onset, which is seen in 50 per cent. of cases. There were also no areas of hyperesthesia.

Her temperature was characteristically irregular. The pulse was likewise slow—another characteristic of the disease—being only 84, with a temperature of 103° F., and 78, with a temperature of 101° F.

Signs of nerve involvement were: Brudzinski's sign (flexion of thighs on abdomen when the neck is bent), Kernig's sign, and increased patellar and triceps reflexes (on the right side only, in this case).

The *tache cérébrale* was seen in this case, but is of relatively minor importance, as it may be present in a number of conditions and is only a manifestation of vasomotor instability.

MacEwen's sign (percussion on the skull) is hard to elicit, and requires one practised in its use to interpret any results.

Finally, the spinal-fluid findings were characteristic. The fluid was turbid, under increased pressure, with an increase in cells and a predominance of polymorphonuclear neutrophils. The albumin was positive and globulin was 4 plus. The spinal

sugar is usually reduced more than it was in this case, which was 55 mg. per 100 c.c. on two occasions (September 24th and 30th).

A remarkable feature of this case was that, with a patient six or six and a half months pregnant, the disease did not bring on abortion, as is the rule with all acute infectious diseases.

As regards cisternal puncture, there are quite a number of opinions. The strongest advocates of the puncture report exceptionally good results with its use, and attribute failures to ignorance of the proper technic, while others report serious accidents following its employment. Locally, it seems to have worked well in this case, but whether recovery was due to this method of therapy future cases will tell.

It would seem that in cases of spinal block (and certainly the tendency is to block the canal with the exudates called forth by the meningococcus), the cisternal puncture is much the easiest and safest method to employ, and offers all the advantages of a trephine with ventricular puncture. Even in those cases without spinal block, the cisterna magna would seem the most logical point to inject the serum, as it would bring the therapeutic agent at once into contact with the most virulent and active point of the infection, and in the greatest concentration. Ayer[18] showed that 30 c.c. of India ink, injected into the subarachnoid space of a cadaver, just blackens the base of the brain, and that 20 c.c. of serum introduced by lumbar puncture does not reach the cisterna magna. We must then ask ourselves, when we employ the lumbar puncture method of serum therapy, do we receive sufficient concentration of serum at the vital points to combat the infection? And, also, if we do not, are not the chances of occurrence of spinal block increased, with the resulting necessity of trephining and ventricular puncture? Cisternal puncture would then appear as a prophylactic measure, in some degree, to spinal block. Ayer[18] further shows that a cisternal puncture with the introduction of 20 c.c. of India ink will stain the entire cerebral cortex, as well as the basilar cisterna. This is rather strong experimental evidence.

Since the meningococcus reaches the cerebral subarachnoid

space through the nasopharynx, it would seem logical to inject the curative serum at the areas first infected. If we have a spinal subarachnoid block, cisterna puncture is imperative.

Ebaugh[19] reports 5 complete recoveries in 8 cases of advanced meningococcal meningitis treated with cisternal puncture. One of his cases had a double block—a spinal subarachnoid block present from the fourth to the tenth day, and a ventricular block from the sixth to ninth day. He treated the case with combined simultaneous spinal, cisternal, and ventricular punctures, introducing 560 c.c. of serum by 18 lumbar punctures; 155 c.c. by 6 cisternal punctures and 75 c.c. by 4 ventricular punctures. The patient recovered with no sequelæ. He says block of the spinal subarachnoid space may be prevented by early cisternal puncture, and that the presence of such a block makes the procedure imperative.

The technic of cisternal puncture, as described by its chief advocates[20] seems simple enough to be employed by the medical man in the routine treatment of his cases. It is given here: The occipito-atlantoid ligament extends from the posterior rim of the foramen magnum to a corresponding position on the first cervical vertebra. The dura lies on its anterior surface. The depth of the reservoir at this level is 1.5 to 2.5 cm. An 18-gage needle, 6 cm. long with a 2 mm. bevel, is used. A point is selected in the midline of the neck just above the spine of the axis. A plane passing through the glabella and upper edge of the external auditory meatus will also pass through this point. The needle is inserted at an inclination slightly greater than this imaginary plane, and is directed upward and inward for an average distance of 4 cm.—it is rarely over 5 or under 3 cm. The feeling when the dura is pierced is characteristic and should be relied upon to determine the point at which to stop the insertion. A graduated needle is not to be used, but rather one with a mark scratched on it at the 5 cm. point, for with a graduated needle a smooth and uniform insertion of the needle is impossible. Ayer showed experimentally that movements of the head did not affect the position of the needle, nor interfere with its position after it is inserted—a point of importance, for,

should the patient make a quick move during the insertion of the needle, it will not do any damage.

Various other positions of spinal puncture have been recorded, but all agree they are much more dangerous than cisternal puncture. Chartier pierced the eighth dorsal space in two instances, while Ravant and Kralunitsky inserted the needle between the sixth and seventh cervical vertebræ.

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CLINIC OF DR. C. McD. SMITH

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A CASE OF ECHINOCOCCUS CYST OF THE LIVER AND THE PERITONEAL CAVITY

MRS. A. G., white, forty-four years old, a native of Western Arkansas, and the wife of a physician; was first seen in the summer of 1917, when she complained of general ill health and discomfort, but had no definitely localized symptoms. Upon examination she was found to be of the asthenic type, above the average height, and to have a loose, thin, flaccid abdominal wall. The liver was distinctly palpable well below the costal border, suggesting a ptosis of the liver or an enlargement of it. There was no tenderness or ascites.

In June, 1919, the patient was seen again after a two-year interval, and gave a history of for several months noticing a mass in the right side of her abdomen, which mass was gradually enlarging. For about six months she had been suffering from abdominal crises, which occurred about once a month, and lasted for from three to six days. During these attacks she had pain and cramps in her abdomen, nausea and vomiting, and diarrhea. She had no fever, had not lost weight, was not jaundiced, and no history of urticaria was obtained. Her general health seemed very good. Examination revealed a large mass in the right hypochondrium causing a distinct bulging of the abdominal wall, and seeming to be rather firm but cystic, as a cyst whose contents were under considerable pressure. The liver could be distinctly felt just above this mass, and its surface presented a few small nodules near the margin. A diagnosis of echinococcus cyst of the liver was made, and operation was advised.

On June 7, 1919 her abdomen was opened and explored. There was a large cyst, attached to the under surface of the right

lobe of the liver, extending medially until the wall of the gall-bladder was involved in the cyst. This cyst had a rather tough translucent wall, and contained approximately 3 liters of a clear, slightly colored fluid; there were also present about a dozen small ovoid cysts from 1 to 2 cm. in diameter, situated in various places on the liver and on the mesentery. They had the appearance of being attached to the outside of the liver rather than of having developed deep within its structure. The large cyst was marsupialized. The cyst wall was sutured to the opening in the peritoneum and was incised, drained, and packed with gauze to bring about obliteration of the cavity by granulation from the bottom. Several of the small cysts were removed from the liver but, owing to the poor condition of the patient, several of them were left. The patient did fairly well until the sixth day after the operation, when she developed an abdominal crisis with nausea, vomiting, cramps, and diarrhea, and during this attack she came very near dying, but recovered and was discharged July 16, 1919, apparently well after six weeks in the hospital.

She remained apparently well until the latter part of 1924, when she noticed a mass developing in the right lower quadrant of her abdomen. This was accompanied by no subjective symptoms whatever. Examination revealed a mass, somewhat larger than a man's fist, in the right lower quadrant of her abdomen. The liver was still palpable, with a few small nodules upon it which were interpreted to be small cysts upon its surface. A laparotomy was performed, and a cyst similar to the one above was found in the mesentery. This cyst was about the size of a quart cup. The cyst was carefully dissected loose and removed intact. The abdomen was explored and several small cysts were present on the liver and in the mesentery. The patient made an uneventful though slow recovery, and was discharged, apparently well, June 14, 1925, after three weeks in the hospital.

Lately, the patient has noticed a mass in the left side of her abdomen in the region of the left kidney. This mass has the generally irregular feeling that one would get from a bunch of

large grapes; which, in the light of the history of the patient, suggests a multiple cystic condition of the left kidney or of the mesentery or omentum. The nodules on the liver are still palpable and there is another nodule slightly larger, softer, and nearer the midline than the others, which has lately appeared. This suggests the presence of another actively growing cyst. The prognosis in this case seems to be pretty bad. The present opinion as to the best procedure is that an exploratory laparotomy should be done to determine the exact location and nature of the new masses, with particular attention paid to the kidneys. If the left kidney is involved and the right is not, it may be removed, but if both are involved she will be let alone.

This case is presented as a rather typical case of echinococcus cyst of the liver. It is of considerable interest, also, that the patient's mother is said to have died of the same disease. This may help to explain the presence of such a condition in a native in a country so far from the usual location of the disease.

Discussion.—Hydatid cysts, hydatid disease, or echinococcic cyst is a comparatively rare disease, but by no means unknown in this country, over 200 cases having been reported in North America up to 1901. It may be defined as a parasitic cystic condition caused by the larval form of the *Tænia echinococcus* of the dog, which may affect any part of the body, but by far most commonly the liver, and which consists usually of one or more mother cysts with internal or external daughter cysts.

Etiology.—The causative agent is an intestinal parasite of the dog, and in the adult form is a tiny cestode 4 or 5 mm. in length, composed, as a rule, of four segments, of which only the terminal one is mature and filled with ova (usually about 5000). Intermediate hosts are many animals, including man, cattle, hogs, and sheep. The sheep is the most important one from the standpoint of being related to human disease, for it is in the regions where there are relatively large numbers of dogs and sheep together that the disease is most common in man. The disease is quite common and endemic in Iceland, the Southern parts of Australia and New Zealand, which are also low and swampy, in European Russia, and in Argentine, in all

of which regions sheep predominate as the domestic livestock. There is a form of echinococcal disease (the multilocular variety) which is prevalent in other localities, notably Switzerland, where large horned cattle are the rule. The two diseases which are caused by parasites which have not as yet been differentiated except by their different lesions and localities of occurrence, do not occur in the same locality, except in a small part of Russia. The first mentioned, or unilocular type, alone will be discussed to any length here, the multilocular type bearing to it the same relation as a malignant, infiltrating tumor to a benign non-infiltrating tumor, whose bad effects are due largely to its position and space encroachment. The multilocular type affects the liver almost exclusively as a primary lesion, although secondary lesions, probably metastatic, may be wide-spread. Close association of people with dogs, or the use of a water supply contaminated by dogs, are regarded as the most important etiologic factors. Residence in an endemic area seems to be dangerous from the fact that in large series of patients admitted to hospitals in Iceland from one-sixth to one-twenty-seventh are cases with hydatids, and it is estimated that about one-thirtieth of the people of this country are infected. In a large series of patients admitted to the Mount Gambier Hospital in Southern Australia, one out of 65 patients had hydatid disease.

Pathology.—This disease affects the liver more often than all the other organs combined, about 70 per cent. of the cases having involvement of the liver. This is probably due to the transportation of the larvæ to the liver by the portal circulation after the ovum is ingested and is hatched out in the intestine of the host and the larva has penetrated the gut wall and entered the blood-stream. The next most common site of cysts is the lungs, and next the brain and the kidneys. They may develop anywhere, including the bones, where they generally make amputation necessary. The cysts may be single, but are quite often multiple, due to either multiple infection, or from an escape of the contents of the cyst, causing secondary metastatic growths. The essential lesion is a cyst which may be of any size up to one containing 3 or 4 gallons of fluid. The cyst wall is quite

characteristic, being a laminated structure made up largely of chitin. It is translucent and pinkish in color in the young cysts, but denser and rather opaque in the old ones. It is lined within by the endocyst, which is a granular, cellular layer which proliferates and forms daughter cysts which are, as a rule, within the cavity of the mother cyst, and it also secretes the fluid contained within the cyst. The daughter cysts in turn grow and their walls proliferate and form grand-daughter cysts, the walls of all these cysts bud or proliferate so as to form brood capsules, and these gradually give rise to little bodies called scolices, which represent the immature heads of the adult type of tæniæ. Each scolex presents four sucking disks and a ring of hooklets which are invaginated until they enter the dog, where they are evaginated to form the adult head, and give rise to an adult worm. By this method of asexual reproduction, a single ovum may produce a great number of potential adult worms, and this is a factor in the preservation of the species. The fluid contained within the cyst contains an albumin not precipitated by heat or nitric acid, and a relatively large amount of sodium chlorid. The daughter cysts and scolices float free within the mother cyst, as a rule. The presence of the cyst seems to excite the formation of a non-inflammatory capsule, fibrous in nature, on the part of the host, and the cyst seems to get its nutriment by absorption from the fluids in and around this capsule. The host and parasite seem to live in symbiosis, and, for this reason, its development is remarkably free from symptoms other than those due to space encroachment. These cysts may terminate their development by rupture, or by death from any of a number of undetermined causes, or by becoming infected and suppurating. Their rupture may make the disease general, or it may mark its end. The common sites of rupture are into the peritoneal cavity with seeding; into the intestinal tract or bile-ducts, or upward into a bronchus and thus out. If the cyst degenerates and dies, it regularly goes through the following stages: First, a turbid stage, due to the precipitation of the colloids of the nutritive pabulum; next, a fatty stage, in which the cyst contents are remnants of membrane and scolices within

a butter-like mass of smegma; next, there is the stage of desiccation, in which the contents are dried to a putty-like mass; and finally a stage of calcareous infiltration, in which hooklets and portions of the redundant membrane may still be found. If the cyst suppurates, it simply becomes an abscess. The life of one cyst is not related to that of another within the body, and cysts in the several stages of decay may be found with living cysts in the same abdomen or elsewhere in the body.

The general pathologic changes of the body are few and inconstant, consisting mainly of attacks of urticaria, which some think are due to the absorption of escaped cyst-contents; a moderate and inconstant eosinophilia; and a change in the blood-plasma resembling an immunity reaction. Owing to this change in the blood, a complement-deviation test and a precipitin test have been devised. The former has a technic similar to that of the Wassermann test for syphilis; the other consists of mixing equal quantities of the patient's serum and cyst fluid, and placing it in an incubator for two hours, when a precipitate indicates the presence of a cyst in the patient's body. The value of these tests is not well established, as some observers claim them to be positive in the absence of the cyst, and sometimes negative in its presence.

Symptomatology.—In general, the development of cysts is very quiet, and they are often found as total surprises at autopsy. The symptoms, other than urticaria, and the blood changes are due to the mass, weight, and space encroachment.

Only cysts of the liver and abdominal cavity will be considered in detail. Jaundice practically never occurs, and is due to occlusion of the bile-ducts by pressure from the outside, or to rupture into them with occlusion by a piece of membrane or a small cyst when colic is present. If the cyst suppurates, the signs of an abscess of the liver supervene, or rather supercede those of an inactive mass in the side. If the cyst is small and deeply situated it may give the impression of an enlarged liver, but, if it attains any considerable size, the cyst emerges from the liver and may be distinguished below the liver, or it may occur higher up and push the liver downward, and give a dome-shaped

area of dulness or flatness extending for a variable distance, which may be considerably up into the chest. As a rule, the patient is in very good health, and presents himself with no symptoms except a mass in the abdomen, which is either rounded or lobulated, tense and fairly smooth, as a bladder containing fluid under considerable pressure. This mass upon percussion is sometimes noticed to give a peculiar vibration which is attributed to the collision of the daughter cysts within the large cyst. The cyst is slow in developing. There may be a sudden recession or disappearance of the mass with rupture of the cyst, and with such an occurrence urticaria, sudden ascites, diarrhea, and symptoms of shock may occur; or the cyst opens upward, which it often does, the patient is seized with an attack of dyspnea and coughing, with a profuse expectoration of the cyst contents, or he may be drowned by the fluid in his bronchi. A cyst may rupture into the abdominal cavity, and cause a persistent ascites with a number of masses developing in the abdomen. Cysts of the liver or spleen may give the physical findings of pleurisy with effusion, except that the shape of the flatness may vary.

The **diagnosis** of hydatid cyst depends generally upon residence in a country where this disease is endemic, and upon the gradual development of a tumor mass which has the characteristics of a rather firm, tense, fluid-containing cyst, which develops without symptoms of dysfunction or of pain, except whatever discomfort may result from the presence of the mass. There may or may not be an eosinophilia. The precipitin test and the complement-fixation test are regarded as having considerable value if they are positive. Hydatid fremitus, if obtained, is rather characteristic, but is said to be obtained in only about 30 per cent. of cases. A positive diagnosis may be made by exploratory puncture and the finding of the scolices and parts of membrane in the fluid, but this is very strongly opposed by most authorities in the face of a probable hydatid cyst, because of the possibility of spreading the disease and because of the marked symptoms which sometimes follow it, such as urticaria, severe shock, syncope, or even death, which symptoms are deemed due to the absorption of escaped cystic fluid. Also

rupture of the cyst has followed puncture. Microscopic examination of the material coughed up, vomited, or passed by rectum in case of rupture into a viscus may lead to a positive diagnosis.

The **prognosis** depends upon the situation and number of the cysts, and upon the individual patient.

Treatment.—There have been many means of treatment tried, including acupuncture, aspiration, aspiration with injection of substances to kill the parasite, incision and drainage, and complete excision. The best methods are complete excision where practical, and in others marsupialization, which is incision and drainage. In the liver the latter is the one usually used.

Prophylaxis for this condition involves avoiding intimate contact with dogs and the securing of a good water-supply, free from contamination, or prevention of the infection of the dogs by careful feeding, and preventing them from eating sources of infection, as parts of sheep which were infected.

Summary.—This is an isolated case of hydatid cyst, in which the patient's mother probably played a part in importing the parasite.

The disease is due to the larval form of an intestinal parasite of the dog family.

The disease is endemic and very common in certain regions, in all of which many sheep are raised and the people come into rather intimate contact with dogs.

The diagnosis depends upon the presence of a tumor with few symptoms.

The disease is chronic and the prognosis depends upon the individual case.

The treatment is surgical—no medical treatment having any effect at all.

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ATYPICAL TUBERCULOUS ADENITIS COMPLICATED BY MULTIPLE TUMORS OF THE BONE-MARROW. REPORT OF A CASE.

A. M., a colored male, aged thirty-three, a native of Louisiana, was admitted to Charity Hospital on September 28, 1926, complaining of an enlargement of the neck of six years' duration. The swelling began on the left side of the neck in front of the angle of the jaw, and, as this progressed, a similar enlargement appeared on the right side of his neck, about eighteen months after the onset. In the third year of his malady the front of the neck beneath the chin began to enlarge, so that the neck became almost encircled by the growth.

The general health of the patient remained good until in April, 1925. At this time he began to experience joint pains, especially in the right hip, pain in the chest, and developed a cough with slight expectoration; the sputum was sometimes bloody, but he believes the blood came from his gums. During the next few months he became very weak and lost weight rapidly, and in November, 1925, was forced to go to bed. He remained in bed for five months, during which time he suffered from joint pains, pain in the chest, and persistent indigestion with nausea and vomiting. He states that his temperature reached 102° F. at this time, and that each morning he experienced chilly sensations. He regained his strength very slowly. It was July before he could walk as far as 200 yards. During all this time the enlargement of the neck became progressively greater, but has never been painful or tender.

In May, 1926, a generalized pruritus set in, which has been quite intense, and has persisted with remissions until the present

Fig. 206.—Shows the bilateral involvement of the neck.

Fig. 207.—The collar distribution is seen in this view.

time. Simultaneously with the itching, a papular eruption appeared on the arms, thighs, and back, which subsided in a few months.

For six months his eyes have been painful, and vision is somewhat blurred.

At the time of his admission the patient complained of weakness, attacks of dyspnea occurring in the afternoon, substernal oppression, and pain in, and partial immobilization of the

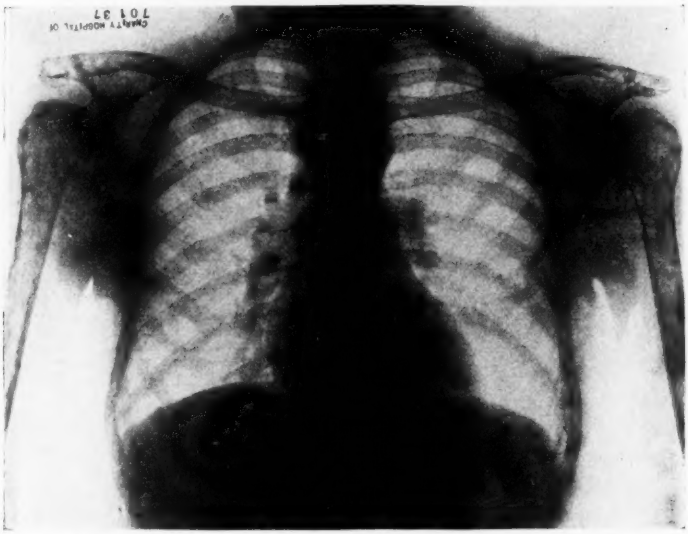

Fig. 208.—Osteoporosities of the thoracic cage and shoulder girdle. Mediastinal nodes not involved.

left shoulder. His weight was 130 pounds, against an average weight of 150 pounds. He has never had any difficulty in swallowing, or any diaphoresis.

The patient was in Pittsburgh, Pa., when his malady began, and presented himself for treatment at the dispensary of the St. Francis Hospital. He "was treated in this dispensary in 1920 and 1922 for enlarged cervical glands. One of these glands was incised, and a draining sinus remained for two months.

No biopsy was made, as the patient did not enter the house, but it was felt at the time that the enlargement was due to a tuberculous adenitis. At the time of his first visit he had a positive Wassermann. He received salvarsan treatments, and on his return, a year or two later, it was negative. It was felt that

Fig. 209.—Osteoporotic changes in the cranial bones.

the enlargement was tuberculous, rather than due to Hodgkin's disease, in its first development."[1]

The patient returned South in June, 1925. While in bed from November, 1925 to March, 1926, he received only medical treatment.

The outstanding feature on physical examination is a marked swelling of the neck on both sides and beneath the chin. Pal-

pation shows the enlargement to be due to lymph-nodes, which are enlarged, firm, discrete, and unattached to the skin or underlying structures. Some of the glands are as large as hen's eggs, others only slightly enlarged. These glands form a collar, extending around the front of the neck from behind the sternomastoid on each side. The supraclavicular glands are also enlarged on both sides. The axillary nodes are not palpable. The inguinal and epitrochlears are slightly enlarged, but not

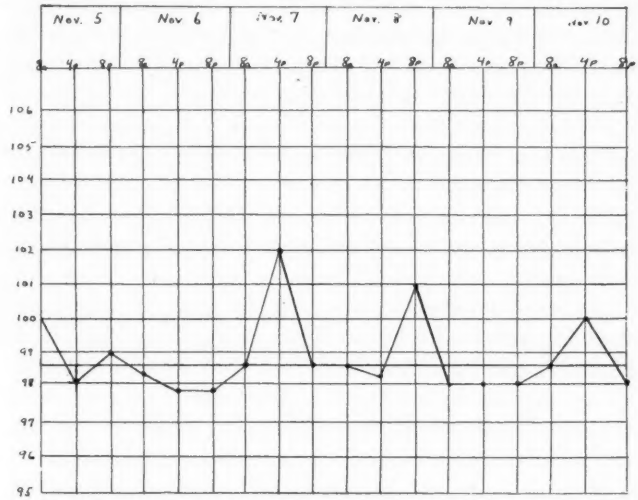

Fig. 210.—The typical temperature curve of this patient. A. M., ward 146, bed 9, Charity Hospital.

more so than is often the case in other subjects, and one gains the impression that these are not involved in the process present in the cervical and supraclavicular glands.

The skin is dry, scaly, and inelastic; no eruption is present.

The eyes present the characteristic features of phlyctenular keratoconjunctivitis. The pupils are equal, round, and react to light and distance.

In the mouth most of the molar teeth are missing. The gums and buccal mucous membrane present a purple discoloration. The tonsils are atrophied, and show no evidence of disease.

The chest is flattened and poorly nourished; the ribs and clavicles are prominent. The right side lags on inspiration. There is pronounced dulness in the right supraclavicular space. Resonance on percussion is impaired in the right axilla, and anteriorly below the clavicle on the same side. Fine inspiratory râles can be heard over both apices. Over the right scapula the breathing approaches the bronchial. At the left base posteriorly the breath sounds are exaggerated, almost cavernous in quality; fine inspiratory râles are heard here. The whispered voice sounds are transmitted down as far as the fifth thoracic vertebra (D'Espine's sign). No signs of mediastinal lymphadenopathy can be elicited by percussion.

The heart is not enlarged; no murmurs are present.

There is a moderate dorsal scoliosis, with the convexity of the curve to the right.

The abdomen is not prominent, soft, and symmetrical. The liver and spleen are not enlarged, and no abdominal glands can be felt.

The patellar reflexes are greatly exaggerated. Babinski's sign is not present. There is slight edema of the ankles. No further abnormalities could be detected on physical examination.

The temperature has been extremely irregular, varying between 97° and 102.6° F. Sometimes it is higher in the afternoon, at other times in the morning. Some days have been apyretic.

The blood-picture has shown considerable variations. There is a moderate secondary anemia, with a total red-cell count varying between 3,500,000 and 4,000,000, a hemoglobin of 55 per cent., and a color index around 0.75. The total leukocyte count has, on the whole, been low, between 3000 and 5500. There is an increase in the percentage of transitional cells (14 to 20 per cent. against a normal of 7.5).[2]

Previous to my observation of the case an increase in the eosinophils was noted (10 and 14 per cent.). In three blood-counts, counting a total of 600 cells, I saw only one eosinophil. The other white cells occurred in fairly normal proportions.

Examination of the feces is negative for ova. The sputum

contains no acid-fast bacilli. The urine shows traces of albumin and a few casts. The Wassermann reaction is negative.

From the history and physical findings, a tentative diagnosis of Hodgkin's disease was made. A skiagram of the chest was requested, to determine whether the mediastinal nodes were involved. The following report was received: "Hilar shadows exaggerated and thickened; hazy, fuzzy infiltration involving the upper lobes of both lungs. Multiple osteoporous areas involving the ends of the bones forming both shoulder-joints, also in all of the ribs on both sides, sternal end of the clavicle, scapulæ, and bones of the head. This is a case of multiple myeloma." A subsequent picture showed a similar involvement of upper ends of the tibiæ.

This report indicated examination of the urine for Bence-Jones protein. I have not been able to demonstrate its presence.

On September 30th and October 19th, small, superficial glands were removed for microscopic study and guinea-pig inoculation. The glands were firm and not necrotic, but a microscopic diagnosis of tuberculous adenitis was made, and a pig, injected on October 18th and killed December 2d, showed tuberculous lesions in several organs, from which acid-fast bacilli were recovered. On December 14th, under general anesthesia, one of the larger, deeper glands was removed, with the idea that this perhaps would show the characteristic picture of Hodgkin's disease. The gland was the size of a hen's egg, soft in the center, and exuded a caseous material on section. Microscopically it showed only the changes of tuberculous adenitis.

The treatment pursued has been rest, sustenance, and irradiation. The patient has received two radium applications at intervals of one month, the first of 900 mg.-hours to each side, and the second of 2300 to the left side and 1800 to the right.

Progress has not been favorable. The size of the glands has diminished somewhat under the radium therapy, but there has been no improvement in the patient's general condition. He has lost 5 pounds since admission. A recent complication is a corneal ulcer of the right eye.

The proper diagnosis of a case such as this entails the consideration of all conditions causing a chronic enlargement of the cervical lymph-nodes. These are: 1. Tuberculous adenitis; 2. syphilitic adenitis; 3. primary and metastatic carcinoma or sarcoma of the lymph-nodes; 4. a group of adenoses of obscure nature, including (*a*) Hodgkin's disease or lymphogranulomatosis, (*b*) lymphatic leukemia, (*c*) pseudoleukemia, aleukemic leukemia, or lymphatic aleukemia, and (*d*) lymphosarcoma. Another condition, leukosarcoma, though not concerned in the diagnosis of this case, belongs in this group as well.

Hodgkin's disease is a term which, properly applied,[3] refers to a progressive enlargement of the lymph-nodes and frequently the spleen as well, presenting a characteristic histopathology, consisting of an early lymphocytic proliferation, and later by the appearance of endothelioid cells and larger mono- and multi-nuclear giant-cells, accompanied usually, but not always, by an abundant infiltration with eosinophils, replacing the lymphoid structure of the gland, and ultimately by fibrosis.[4] Clinically it is characterized by progressive enlargement of the lymph-nodes, the nodes usually remaining discrete and freely movable, frequent enlargement of the spleen, and a gradually developing anemia and cachexia.

Lymphatic leukemia is one of the blood dyscrasias, and is characterized by an enormous increase in the circulating lymphocytes, together with a simultaneous universal enlargement of the lymph-nodes, and lymphocytic invasion of the parenchymatous organs, muscles, and bone-marrow.

Pseudoleukemia or aleukemic leukemia is a condition identical with lymphatic leukemia, but without the blood changes.[5]

Lymphosarcoma is a "more or less wide-spread growth, arising from a group of glands or from a tract of lymphoid tissue," which rapidly breaks through the capsule of the gland and invades the surrounding tissues, but with only slight tendency to metastasis.[6] Histologically this tumor consists of embryonic lymphocytes enclosed in a delicate fibrous reticulum.

Leukosarcoma is a very invasive and destructive tumor,

which arises in some organ or tissue, composed of lymphoid cells which seem to escape into the blood-stream and give rise to a leukemic blood-picture.[7]

As regards the nature and etiology of these diseases and their relation to each other, a great deal of confusion exists. The majority of authors today recognize Hodgkin's disease as a pathologic entity, though some consider it a term of clinical origin and not corresponding to a definite histologic lesion.[8] It bears many of the earmarks of both an infection and a neoplasm, and much controversy has arisen over which group it should be placed in. Most writers at present consider it to be a granuloma rather than a new-growth. The advocates of its infectious origin are divided into two schools, one believing it to be a manifestation of tuberculosis, the other believing it to be non-tuberculous. In connection with this case, which, clinically, presents many signs of Hodgkin's disease and, pathologically, is tuberculosis, a discussion of the relation between these two diseases would be very appropriate, but the restricted length of this paper will not permit such a discussion. Suffice it to say, that although most pathologists deny the tuberculous nature of Hodgkin's disease, there is a close association between the two affections, and it seems probable that at least certain cases of Hodgkin's are produced by the tubercle bacillus.[9]

The same divergence of opinion exists as regards the nature of lymphosarcoma, leukosarcoma, lymphatic leukemia, and pseudoleukemia. All may be subvarieties of one disease, or each may be a separate entity. They may be neoplastic or infectious; they seem to partake of the nature of new-growths rather than of infections.

One cannot help but consider the possibility that these obscure diseases may represent transition steps between the infectious granulomas and neoplasms.[10] Tuberculosis presents only the characteristics of an infection, and is known to be an infection. Hodgkin's disease resembles tuberculosis closely, but also has many of the characteristics of a new-growth, and is considered as such by some authors.[11] Lymphosarcoma and lymphatic leukemia approach the neoplasms more closely. The

next step is leukosarcoma, which has nearly all the earmarks of a neoplasm, and from here the transition is very small to round-cell sarcoma, a recognized neoplastic tumor. This brings us into the field of the infectious theories of the origin of neoplasms, which is quite out of the scope of this paper.

Multiple myeloma is a multiple, destructive tumor of the bone-marrow, which invades the cortex of the bones and produces pathologic fractures. Histologically, there are two types, the plasma-cell and the myeloid forms. The favorite site of myeloma is the flat bones. It involves the ribs, sternum, and pelvis chiefly, but the vertebræ, cranium, femur, clavicles, and humerus may be attacked as well.[12] It is slow-growing, but universally fatal, death occurring in from a few months to several years. Chiefly males are attacked, in the fourth and fifth decades of life. It is characterized, clinically, by vague pains in the bones and a gradually developing anemia and cachexia, with the occurrence of spontaneous fractures. Hyperactivity of the deep reflexes has been described.[13] The presence of Bence-Jones protein in the urine is an inconstant finding in multiple myeloma, occurring in less than one-half the cases, and its presence may be periodic.[14] It may occur also in some of the leukemias, myeloma, osteomalacia, carcinoma of bone, and chondrosarcoma.[15]

It is interesting here to note that Hodgkin's disease sometimes presents multiple bone-metastases, with the occurrence of pathologic fractures.[16] It is quite possible that such metastases might be indistinguishable from the Roentgen-ray picture of multiple myeloma. Altschul, in discussing a case of sporotrichosis involving the bone-marrow, stated that "the apparently characteristic Roentgen-ray pictures of multiple myeloma are not always necessarily due to true tumors, since an infectious granuloma can also call forth similar pictures."[17]

In the diagnosis of this case, the differential points between the conditions enumerated must be considered.

Syphilitic adenitis usually appears in the secondary stage, with painless enlargement of the posterior cervical nodes, together with other signs of syphilis. The continued enlargement

of these glands under antisyphilitic treatment definitely rules out syphilis.

Primary neoplasms can be diagnosed only by biopsy; if secondary, the primary growth may be observed. Biopsy in this case has precluded the possibility of carcinoma or sarcoma.

The absence of general glandular enlargement and of splenomegaly rules out leukemia and pseudoleukemia. In these affections the entire lymphatic system is involved simultaneously;[18] in the former there is a leukemic blood-picture.

The character of the nodes in this case, discrete, movable, unattached, is unlike the picture of lymphosarcoma, where surrounding structures are rapidly invaded. Histologic examination has also proved that this disease is not present.

The diagnosis therefore rests between tuberculous adenitis and Hodgkin's disease, and the differential points between these will be enumerated:

1. Age of onset: Tuberculous adenitis usually occurs in childhood. Hodgkin's disease may occur at any age, but is most common in the third and fourth decades.[19] The age of onset in this was twenty-six, in the third decade.

2. Sex: Sex preference is not marked in lymphatic tuberculosis. About two-thirds of all cases of Hodgkin's disease occur in males.[20] This case is in a male.

3. Race: Tuberculous adenitis is very common in the negro. Hodgkin's disease is not common in the negro.

4. Prognosis: Tuberculous adenitis runs a chronic course, and tends to spontaneous healing,[19] seldom of itself proving fatal. Hodgkin's disease is almost universally fatal, most cases dying within five years,[21] though cases lasting as long as eleven years have been reported,[22] and some cures have occurred. This case is of almost seven years' duration, and the prognosis seems to be bad.

5. Site and character of adenopathy: In the neck, tuberculosis usually begins in the anterior triangle[23] and remains unilateral.[24] The glands usually soften and break down, becoming adherent to the skin, and draining sinuses remain. This is not always the case, however, for tuberculous glands may remain

firm and discrete.[25] General adenopathy due to tuberculosis is uncommon, but sometimes occurs.[26] Hodgkin's disease usually first involves the glands behind the sternomastoid or the supraclavicular nodes; it is usually bilateral, and forms an encircling collar.[27] The disease is usually progressive to other nodes (axillary, mediastinal, inguinal), though beginning in a single group. The involved glands are usually, but not always discrete, larger than tuberculous glands, elastic in consistency, and unattached to the skin.[28] In this case the primary site of enlargement was in the anterior triangle, but the involvement at present is bilateral, extending behind the sternomastoid on each side, and the supraclavicular nodes are involved. The glands are discrete and freely movable, but a sinus persisted after an incision in 1922. There is evidence of some mediastinal involvement,[29] but so slight as to suggest tuberculosis rather than Hodgkin's disease, in which condition the enlargement is much greater, as a rule.

6. Splenic enlargement: This is not common in tuberculosis. It occurs in a majority of cases of Hodgkin's disease,[30] but is usually slight.[31] There is no splenic enlargement in this case.

7. Fever: Not given as a symptom of lymphatic tuberculosis until suppuration occurs.[32] If pulmonary tuberculosis is also present, one would expect the usual intermittent fever of tuberculosis. Fever is always present at some time in the course of Hodgkin's disease. It may be of any type, but is most often intermittent or paroxysmal, frequently accompanied by chills and sweats. It may be higher in the morning than in the evening. There may be periods of apyrexia.[33] This description fits the type of fever observed in this patient fairly closely, except that there have been no sweats.

8. Pruritus: Skin itching is not mentioned in connection with tuberculosis. It is given as one of the cardinal symptoms of Hodgkin's disease,[34] the others being tumor masses, fever, and weakness. Eruptions also frequently occur in Hodgkin's disease. Both pruritus and skin lesions are symptoms here.

9. Cachexia and loss of weight: These accompany suppuration in tuberculous adenitis. Both are very marked in Hodg-

kin's disease. They occur in this case without external evidence of suppuration.

10. Irritation of eyes, nose, and throat: Inflammation of the eyes, occurring in this case, is mentioned as a symptom in the diagnosis of Hodgkin's disease. It probably has little differential value, as affections of the eyes are very common in debilitated individuals. Diseased tonsils are undoubtedly the port of entry for the tubercle bacilli in many cases, but have also been suggested as a source of infection in Hodgkin's disease.[35] There is no evidence of tonsillar disease in this case. Carious teeth, present here, have also been suggested as a portal of entry.

11. Blood-picture: The blood-picture in tuberculosis is not characteristic. There is said to be a leukopenia with a relative lymphocytosis.

Bunting considered the blood-picture of Hodgkin's disease characteristic, but most observers deny that it is of very much value in the diagnosis. Bunting described an increase in the blood-platelets and transitional leukocytes, occurring throughout the course of the disease, with an increase of the lymphocytes early in the disease, the total count being normal or slightly increased, followed by a decrease in the lymphocytes and a moderate eosinophilia, with a marked neutrophilic leukocytosis toward the end.[2] This case shows an increase in the transitional cells, and an eosinophilia has been observed. The platelets are not increased. The total count is, on the whole, low.

12. Histopathologic appearance: This cannot be discussed here, but it may be said that at times the two simulate each other very closely.[36] The final diagnosis always depends on microscopic examination, as only one-third of the cases presenting the clinical picture of Hodgkin's reveal the pathognomonic microscopic appearance on biopsy,[37] and glandular tuberculosis may simulate Hodgkin's disease in every clinical feature.

As regards the age of onset, the sex, the character of the adenopathy, the type of fever, the presence of pruritus, and the blood-picture, this case seems to be one of Hodgkin's disease. The race of this man, the site of primary enlargement, the signs of pulmonary tuberculosis, and the absence of spleno-

BLOOD-PICTURE, A. M., WARD 146, BED 9, CHARITY HOSPITAL

Date	September 30, by Charity Hospital.	October 4, by Charity Hospital.	October 26, by J. H. W.	November 5, by E. H.	November 31, by E. H.	January 7, by E. H.			
Hemoglobin	55 per cent.	..	55 per cent.	50 per cent.	55 per cent.	55 per cent.			
Erythrocytes	3,685,000	..	4,000,000	3,500,000	3,830,000	3,965,000			
Color index	..	..	..	..	0.74	0.75			
Total leukocytes	3000	..	4000	12,750	5500	3000			
Small mononuclears	28	24	24	19	8	32			
Large mononuclears	8	20	26	2	11	3			
Neutrophils	68	40	40	79	80	65			
Eosinophils	2	14	10	0	1	0			
Basophils	2	2	0	0	0	0			
Platelets	..	..	..	150,000	..	200,000			
Transitional leukocytes	..	..	..	14	20	6			
Other leukocytes	..	..	..	86	80	94			
Pathologic cells	..	..	..	0	0	0			

URINALYSES, A. M., WARD 146, BED 9, CHARITY HOSPITAL

Date	October 1.	October 16.	November 20.	January 7.					
Clarity	Cloudy.	Hazy.	Clear.	Clear.					
Reaction	Acid.	Acid.	Acid.	Acid.					
Specific gravity	1.020	1.021	1.025	1.034					
Albumin	0.05 per cent.	Slight trace.	Negative.	Negative.					
Sugar	Negative.	Negative.	Negative.	Negative.					
Acetone	Negative.	Negative.	Negative.	Negative.					
Diacetic acid	Negative.	Negative.	Negative.	Negative.					
Indican	Trace.	Trace.	Negative.	Negative.					
Microscopic	Few granular and hyaline casts.	As on Oct. 1st.	Negative.	Few fine, granular casts. Occasional pus cell.					

On October 7th the pathologic department of Charity Hospital reported Bence-Jones protein present. I have never been able to demonstrate its presence. Dr. J. H. Watkins tested the urine for it nine times; eight times the test was negative, the other time the reaction was doubtful.

megaly point to lymphatic tuberculosis. The clinical data, therefore, favor a diagnosis of Hodgkin's disease, but biopsy has proved the tuberculous nature of the lesions. Tuberculosis and Hodgkin's disease are quite often coexistent,[38] but this cannot be assumed to be the case unless nodes showing the Dorothy Reed picture can be found. The tumors of the bones could well be metastatic Hodgkin's disease, but again such an assumption is not justified in the absence of a Hodgkin's picture in the lymph-nodes, and these tumors must be considered as part of a process independent of the cervical adenopathy. The joint pains and cachexia are probably due largely to the myeloma.

This case, then, must be considered as an atypical case of tuberculous adenitis, with multiple myeloma developing independently.

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ANALYSIS OF EIGHTY-EIGHT CASES OF RHEUMATIC FEVER. COMPARISON WITH OTHER ANALYSES, AND DISCUSSION

RHEUMATIC fever presents itself to the world and the medical profession as a problem worthy of serious consideration, due to the frequent cardiac involvement, which often leads to some degree of incapacitation of the individual. The economic importance of heart disease is well shown by the statistics from the Surgeon General's Office, showing that 2 per cent. of all the men examined for the National Army during the World War were rejected on account of heart disease.[1] Again, 2 per cent. of New York City's school children have cardiac disease,[1] and most of these cases are due to rheumatic fever.[3] In Boston, Cabot found rheumatic fever as the etiologic factor of 46 per cent. of 600 clinical cases of cardiac disease.[2]

When this study was begun, the primary purpose was to come to some definite conclusion as to the relative frequency of rheumatic fever in the negro and the white, and to see if some reason could be found for any difference that might exist. Although the results as to the primary object are not entirely satisfactory, due to the fact that the records do not give the necessary information as to the mixture of negro and white, several other points have been brought out. which probably have a more important bearing on rheumatic fever in the South.

The analysis covers all cases of rheumatic fever, 88 in number, admitted to Charity Hospital, New Orleans, La., over the five-year period, January 1, 1922 to December 30, 1926, inclusive. During this period there were 115,213 admissions

(surgical and medical), giving the occurrence of rheumatic fever as 0.076 per cent.; or 1 to every 1309 admissions. Table I gives more in detail the relation to total admission, also as to sex and color.

TABLE I

	Admissions.	Per cent. rheumatic fever.	Ratio of rheumatic fever to admissions.
Female	58,693	0.073	1 : 1365
Male	56,520	0.079	1 : 1255
Colored	52,461	0.064	1 : 1543
White	62,452	0.088	1 : 1075
Total	115,213	0.076	1 : 1309

Color.—Of the 88 cases, 34, or 39 per cent., were colored, and 54, or 61 per cent., were white. This and the relation to admissions, as shown in Table I, certainly are some indications that rheumatic fever is less frequent in the negro race. It was impossible to determine the mixture of white and negro blood occurring in those listed as negroes, and probably the number of pure negroes was small. However, it seems to indicate that there is some racial immunity possessed by the negro, as there are no environmental or other conditions existing which would explain the difference. It was noted that the clinical severity of the disease was no less in negroes than in whites. J. E. Wood, Jr., and coworkers[2] state that the incidence of rheumatic heart disease in 177 cases was 12 colored, where the admissions to the hospital were negroes 1 to whites 3.3. This seems also to show that negroes have some racial immunity. H. C. Bussiere and L. J. Rhea[3] did not discuss the occurrence in negroes, but state that in their analysis of 100 cases, 25 per cent. were Hebrews, which percentage was high in proportion to the population of Hebrews in Montreal. This suggests that there is an influence by race on the disease, or rather there is some degree of racial immunity.

Sex.—There were 45 males, or 51.1 per cent., as compared to 43 females, or 48.9 per cent. In relation to the male and female admissions, the disease seems slightly more prone to affect males than the percentage of the cases shows. However, the difference is so slight between the sexes and in view of the

number of cases, it would be best to consider that sex plays a minor rôle. This, however, compares very favorably with Mackie's[1] analysis, in which he had 198 males and 195 females.

The above includes all ages and, to avoid any criticism, it would be well to state that the Montreal series (Bussiere and Rhea[3]) on children under sixteen years of age gives 61 per cent. females and 39 per cent. males.

Age.—From Table II it is readily seen that the greatest incidence in this series, 25.6 per cent., occurs between the ages of fifteen and twenty years, and that 58.6 per cent. occurs between the ages of fifteen and thirty years. However, the most interesting point is that there was no case recorded under ten years of age. In Mackie's[1] analysis of 393 cases he found 61 in children under ten years of age. Certainly there is no intention of saying that rheumatic fever does not occur here under ten years of age, as I recall, at the moment, seeing 3 cases of mitral stenosis in the past few months in children under ten years of age. The fact that there were no cases under this age will be considered and partially reconciled in the final discussion.

TABLE II

AGE INCIDENCE

Age in years.	Number of cases.	Percentage.
0–10	..	0
10–15	8	9.0
15–20	22	25.6
20–30	29	33.0
30–40	9	10.0
Above 40	20	22.4

Season.—In this series, 68.5 per cent. of the cases occurred in the first half of the year. As in other series, the highest incidence occurred in the spring season, 40 per cent. occurring during March, April, and May. Chart I shows the seasonal occurrence here as compared to that occurring in Montreal.[3] It is very striking to note that the two curves are almost identical, and that, in both, 40 per cent. of cases occurred during March, April, and May.

Temperature.—The temperature charts showed daily rises and

falls as is given in text-books. [5, 6, 7] The mean temperature was not determined, as the estimation of the average temperature

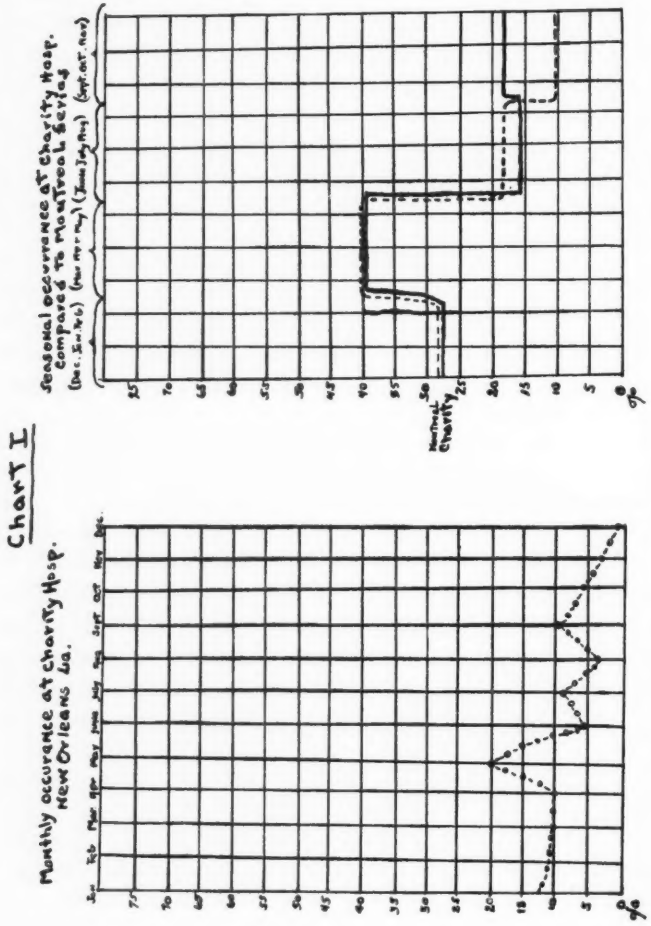
Chart I
Seasonal occurrence at Charity Hosp. Compared to Montreal Service
Monthly occurance at Charity Hosp. New Orleans La.
Montreal Charity

during the febrile period for each case serves our purpose very well. Four cases having typical joint involvement ran a practically normal temperature—18 had between 98.6° and 99° F.,

26 between 99° and 100° F., 27 between 100° and 101° F., 10 between 101° and 102° F., 1 had 103° F., 1 had 104° F. Only 1 case went over 104° F., and in this case the temperature rose gradually to 109° F. and the patient died. It was the only case of death in the series.

Most authors give the average temperature as from 102° to 104° F. for adults. The Montreal series[3] gives the temperature in children as averaging from 99° to 100° F.

This shows very definitely that rheumatic fever here, and probably over the entire South, has a lower temperature than in other sections of the country. This point will also be carried to the final discussion.

Pulse.—Pulse rate has followed fairly closely the general law of a rise of 10 beats to each degree of fever, and so shows nothing of particular interest. The average pulse rate during the acute symptoms is given in Table III.

TABLE III

Pulse rate.	Number of cases.
70– 80	1
80– 90	24
90–100	31
100–110	18
110–120	11
120–130	2

Skin Lesions.—There is no record of any case showing skin lesions. In the Montreal series[3] erythema nodosum occurred in 17 per cent., and purpura hemorrhagica in 4 per cent. of cases. The percentage as given is too high to say that these occurrences were accidental, so then they must have some relation to rheumatic fever in Montreal. Hence, we must say that skin lesions do not frequently occur in this section, and try to explain it in the final discussion.

Subcutaneous Nodules.—This was another sign which was lacking in this series. I would hesitate to say that it did not occur, however. This manifestation has been greatly stressed by English authors, and some American clinicians have found it quite often.

Sweating.—This symptom was recorded in only 9 cases. I am of the opinion that these cases were recorded only because they were marked, and probably that sweating occurred in many other cases, but was not particularly annoying. However, we should not expect the typical severe sweats that are usually described with the disease, because we have just mentioned that our temperatures were lower.

Previous Attacks.—The case histories gave 14 cases, or 16 per cent., as having one previous attack; 4 cases, or 3.9 per cent., two attacks; 3 cases, or 3.2 per cent., three attacks; and 2 cases, or 1.9 per cent., five attacks. The total of 24 per cent. had one or more attacks. This is much lower than occurred in Mackie's[1] analysis, in which he found 47 per cent. This also tends to substantiate Harrison and Levine[4] in their idea that possibly patients suffering from rheumatic fever might be relieved to some degree by moving to a section of the country where the incidence of the disease is less.

Familial Incidence.—Only 4 cases gave a positive history of other members of the family having had the disease. This is only 3.9 per cent., which is exceptionally low as compared to the Montreal series,[3] which gave, in an analysis, 17 per cent. In view of the fact that the infectious nature of the disease has not been proved, no definite significance can be placed on this. However, if one chooses to accept the infectious theory, then this difference would certainly suggest that climatic conditions here are not so favorable for the transmission of the disease as in northern sections of the country.

Focal Infections.—The tonsils seem to be a point of discussion in all articles on rheumatic fever, whether they are considered as a focus of infection or a portal of entry. Fifty-two cases, or 60 per cent. of this series showed the tonsils diseased. Mackie[1] has carefully studied this point, and, in his analysis, 58.8 per cent. of 231 cases showed diseased tonsils, and in only 27.5 per cent. of a control series of 400 cases did tonsillitis occur. His control cases were selected at random from patients in the hospital. This shows that diseased tonsils occur about twice as often in patients suffering from rheumatic fever as

those suffering from other illness. Mackie has gone further to point out the effect of tonsillectomy on recurrences. Of those not having tonsillectomy performed, 60 per cent. suffered recurrences, those having tonsillectomy after the attack showed 40 per cent. recurrences, and those having tonsillectomy before the attack did not have recurrences.

There was poor dental hygiene in 48.9 per cent. of this series. However, without control series this point proves of little value, because of the realization of the fact that many of this class (charity patients) are very careless in dental hygiene.

Blood.—Twenty of the 88 cases had red blood-counts, and in these anemia was noted as follows:

Number of cases.	Degree of anemia.	Per cent.
7	4 to 4.5 million	35
7	3 to 4 "	35
1	2 to 3 "	5

This would tend to indicate that rheumatic fever was often accompanied by a severe anemia. However, I chose to believe that such a conclusion would be faulty for two reasons: first, that red blood-cell counts were probably only done on those cases which appeared anemic; and, second, it is not uncommon normally to find a moderate degree of anemia in this climate. It is, of course, true that anemia occurs in rheumatic fever, but not to the extent that 35 per cent. have a count of between 3,000,000 and 4,000,000.

The cases having leukocyte counts showed usually between 10,900 and 15,000, which is the same as is usually given by standard text-books.

Chorea.—Not a single case of rheumatic fever was recorded as being associated with chorea. It is conceded that the two are often associated, and it seems that the condition here may have been unrecognized.

Heart.—The discussion of this part of the analysis shall only be considered under a general topic of cardiac involvement. Not that the gravity of this part of the disease does not deserve detail consideration, but rather that such a consideration would

deserve an entire paper to itself. The following, Table IV, however, will give the location and type of physical signs on which cardiac involvement was based:

TABLE IV

CARDIAC INVOLVEMENT

	Number of cases.	Percentage.
I. Total involvements	45	51.1
II. Enlargement	22	25.6
III. *Murmurs:*		
A. *Apex:*		
1. Systolic	32	37.0
2. Diastolic	2	2.0
3. Systolic and diastolic	4	3.9
B. *Base:*		
1. Systolic	7	8.0
2. Diastolic	1	0.9
IV. *Thrills:*		
A. Apex	1	0.9
B. Base	1	0.9

Here we see that heart involvement occurred clinically in 51.5 per cent. of cases. In the Montreal series[3] cardiac involvement occurred in 64 per cent. of cases, mitral endocarditis in 70 per cent., mitral and aortic endocarditis in 12 per cent. In Mackie's[1] analysis, cases between five to ten years showed 78 per cent. involvement, and between ten and fifteen years, 79.2 per cent. The percentage of our cases cannot be compared directly to the other series here mentioned, as they specify age and our series takes in all ages. I am of the opinion that frequency of cardiac involvement decreases with age.

Both Mackie's[1] and the Montreal series[3] give a high percentage of recurrent attacks, in comparison to recurrences in this series. This may account for the more frequent heart involvement in their series.

It is also possible that the disease is of a more mild character in the South, and in such a case the frequency of heart involvement might be less.

Arthritis.—Table V gives the frequency of involvement of the various joints in this series, as compared to the Montreal Series.[3]

TABLE V

	Charity Hospital	Montreal Hospital
	Percentage.	Percentage.
All large joints, one after another	84	56
Ankle and knee	0	17
Ankle alone	0.9	17
Knee alone	3.9	5
Elbow alone	0.9	0
Wrist alone	2.0	5
Elbow, shoulder, and wrist	3.9	0
Total	95.6	100

The difference here is not of great importance, and, beside, this series covers all ages, while the Bussieres and Rhea analysis is on children under sixteen years of age. It is to be remembered that arthritis is not commonly as severe a symptom in children as in adults; as a matter of fact, I believe Table V exemplifies this, by the great difference in the number of cases which show a progressive involvement of all large joints.

Duration of Acute Symptoms.—Most text-books give the average duration of acute symptoms as from three to four weeks. This analysis shows the average duration in this series from ten to twenty days. Those remaining over thirty days were for the most part cases being treated for other chronic disease which was found after admission.

Table VI gives more exactly the duration.

TABLE VI

Number of days.	Number of cases.
5–10	24
10–20	25
20–30	21
Over 30	13

Regional Distribution.—It is clearly shown by Table I that rheumatic fever is not such a frequent disease in this section. When compared with northern cities, as is shown by Harrison and Levine,[4] the disease can almost be considered rare. It is well stated by the above authors in their conclusion in which they say, "Rheumatic fever and rheumatic heart disease are

much more common in Boston than in Richmond, Oklahoma City, New Orleans, or Galveston. Baltimore and St. Louis occupy intermediate positions."

Discussion.—As has been previously stated, rheumatic fever is a disease worthy of serious study, and in the North a great deal has been done on the subject. It appears that in the South there has been very little work done, because the disease is said not to occur commonly in this section.

I believe that rheumatic fever occurs more commonly in the South than is believed. Dr. G. R. Herrmann says mitral stenosis is certainly more common than is generally believed. Rheumatic fever is practically the sole cause of mitral stenosis. This point will be borne out surely, as soon as the cardiac clinic, which has been organized for only two years, can have their records cross indexed. Due to the fact that they are not cross indexed, it is not possible to give figures to support the above opinion.

The analysis and comparative study shows, I believe, that rheumatic fever does not have as severe clinical manifestations in the South as is given when occurring in northern sections. To recapitulate these points leading to such a conclusion:

1. The fever is 2° F. less than is given by standard text-books.
2. No case showed skin lesions.
3. Recurrences are about one-half as common.
4. Familial incidence is one-fourth as common.
5. The duration of acute symptoms on the average is ten to twenty days, as compared with the twenty-one to twenty-eight days usually given by text-books.
6. The heart involvement is less, and may or may not have some bearing on the question.

With the clinical symptoms being less severe, it is most probable that there are many cases which do not come under observation or pass undiagnosed.

Bussiere and Rhea[3] state that the temperature in children in Montreal is only from 99° to 100° F. If, then, we encounter in this section rheumatic fever in adults which is 2° F. lower than is generally given as average, we are then likely to encounter temperatures in children as being normal, or very slight eleva-

tions. Also, the fact that no case was recorded as rheumatic fever in a child under ten years of age is very suggestive that symptoms in children may be so slight that they are overlooked. There were over 8000 children admitted during this period under twelve years of age. I think it is very probable that we have many cases occurring in children, and possibly young adults, that are manifesting themselves in atypical forms, such as severe tonsillitis, general body aches, and "growing pains." Such cases are to be sought for, as it is well known that the important sequelæ of permanent cardiac damage bears no relation to the clinical severity of the disease.

The fact that chorea has not been associated in this series offers only two possibilities: First, that there were no children under ten years of age, and chorea is more prone to be associated in the young; second, chorea has failed to be diagnosed in association with rheumatic fever. Other series show as high as 27 per cent. association. I believe physicians of the South should be on their guard for rheumatic fever in atypical forms. Make record of such cases, and in a few years definite conclusions could be reached on this subject.

Summary.—1. Colored are less frequently affected than white, due, probably, to some degree of racial immunity.

2. The occurrence in male and female is practically equal.

3. No case occurred under ten years of age, and the highest incidence is between fifteen and twenty years.

4. The seasonal occurrence is almost identical to other sections of the country.

5. The temperature averages 2° F. lower than usually given for adults.

6. Skin lesions are not a common occurrence.

7. Previous attacks are one-half as common as in northern cities, and familial incidence only one-fourth as common.

8. Tonsils are undoubtedly a focus of infection as proved by Mackie,[1] and this analysis shows 60 per cent. diseased.

9. Chorea associated was not diagnosed in a single case for some unexplainable reason.

10. The heart is probably less often involved than in north-

ern cities, possibly because of less recurrent attacks or less severity of the disease.

11. A high percentage of cases show progressive involvement of all large joints.

12. The duration of acute symptoms is only ten to twenty days, as compared with three or four weeks, usually given.

13. Rheumatic fever in typical form is not as common as in northern cities (Harrison and Levine[4]).

14. Rheumatic fever clinically is less severe in its symptoms.

15. Possibly many atypical cases occur in the forms of tonsillitis and general body aches.

16. More attention should be paid to rheumatic fever in the South.

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CLINIC OF DR. M. MALLOWITZ

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THE RESIDUALS OF EPIDEMIC ENCEPHALITIS

ENCEPHALITIS lethargica can be truly called a new disease. In 1917, René Crucher first described the condition of "subacute encephalomyelitis," which later became universally recognized as encephalitis lethargica. The same author also called attention to the protean manifestations of the disease, particularly the remote sequelæ, and of these latter, the so-called (probably incorrectly so) postencephalitic Parkinsonism. Since that time the literature has become a bulky repository for innumerable contributions in all languages. American clinicians, it may be said to their credit, have played a prominent part in the elucidation of many phases of this condition.

Concerning the etiology there are many conflicting opinions. Most investigators are convinced that a filterable virus is the causative agent. According to Williams, it is a small diplostreptococcus, which may be present in very minute or even filter-passing forms. Rosenow, who has isolated streptococci in so many conditions, has here, too, recovered a streptococcus with a selective action on the central nervous system. We must not confuse the encephalitis due to known agents (pyogenic organisms, yeasts, virus of measles, et al.). There may, however, be some relationship of what we commonly term "flu" to encephalitis lethargica, if we are to draw any conclusions from the relative frequency with which patients date the remote effects of the malady to an attack of influenza.

What is the pathology which produces the remarkable polymorphism of this disease? There are already several scores of necropsies on record and, although controversy exists on certain points, the histopathology both as to nature and location

is pretty definitely settled. In the first place the lesions are always multiple. Hohman found, in all his cases, persistent signs of acute and subacute inflammatory reaction after months and even years of the disease. Two of the patients at Charity Hospital presented themselves five years after the initial attack of fever. For this reason—that is, the ability of the virus to lie dormant in the nervous system—it has been suggested that the term "postencephalitic Parkinsonism" is a misnomer. The typical histopathology is that of perivascular cell-infiltration, hemorrhages, exudation, areas of degeneration, and destruction of nerve-cells.

It was originally believed that the virus produced a selective atrophy of the motor cells of the globus pallidus, with diminution in their number. Later it was believed that the substantia nigra was the seat of greatest atrophy, depigmentation being a frequent finding. Using micrometric methods, McKinley and Gowan undertook a study of the quantitative amounts of cell destruction in both regions. They showed the changes to be minimal in the globus pallidus, and maximal in the substantia nigra, concluding that the essential factor in the production of the Parkinsonian syndrome was the destruction in the substantia nigra, the changes in the globus pallidus being merely incidental findings.

The mode of onset of symptoms is quite characteristic. Usually there is an acute attack of fever, generally resembling that of influenza. The acute, encephalitic attack is characterized by remissions and exacerbations, lasting from days to months. Common concomitants are disturbances of consciousness, ocular disorders, especially diplopia, and a variety of motor and sensory disorders. Within a variable period of time after the subsidence of the acute symptoms, the patient returns to a state of normalcy or near normalcy. Few, if any, signs may be present in this state. A striking feature in the cases I have seen has been the complaint of weakness and ease of fatigue. These people are not as energetic as before their acute attack. they complain of a feeling of hebetude, and pains and aches in various parts of the body. Then gradually the patient's friends begin

to observe changes. The fixed, facial expression becomes evident. Little by little, there is the development of the various sequelæ, notably Parkinsonism.

Of 19 cases which I have reviewed, the earliest case came to the hospital within six months after the acute attack, the latest case five years after an attack. Fourteen of the patients were in the third decade, and only 2 were above forty. Males predominated over females, there being 14 of the former and 5 of the latter. The complaints were many and diverse, with more than one complaint a common thing. Nervousness and tremor were common. Speech defects such as stuttering, a slowness in commencing to speak, and scanning speech were common. Somnolence was well marked in several cases. Mental symptoms were by no means uncommon. There was impairment of gait, and ocular symptoms were quite often encountered.

Typical encephalitic Parkinsonism has been designated the bradykinetic syndrome by Cruchet. The principal features are the following:

1. *Immobility.*—The face is expressionless and fixed. This is the so-called Parkinsonian or Charcot mask, and various descriptions have been given of it. It has been called mummy-like and ironed-out, and compared to a waxen image.

2. *Attitude.*—This is fixed and wooden. The body is bent forward, the neck sunk between the shoulders, the trunk stiff, and the arms slightly flexed on the forearms.

3. *Slowness of Movement.*—The bradykinesia is probably the most important symptom. These patients slowly perform all the normal acts of life, such as: moving, talking, and thinking.

4. *Paradoxic Kinesia.*—By this term is meant the propensity to bend the trunk forward, and to pass from a walking to a running gait, the steps becoming quicker and shorter.

In addition to the bradykinetic syndrome, other residuals may be present. Practically every Parkinsonian shows some mental disturbance. The most common is an emotional disturbance. Early, there may be irritability and bad temper, there may be exhilaration, and depression of a milder type than that seen in manic-depressive psychosis. The patients are

often anxious and harassed. In advanced cases, or in those moribund, confusion or even dementia are prominent. Hohman has carefully analyzed 18 cases, with reference to this phase of the disease. Psychobiologic rigidity or inactivity was prominent. Hypochondriasis was an almost constant feature. Others were of a restless, irritable nature, and only one was violent.

Among other manifestations along with the hypokinetic state are signs of nerve-tissue involvement. This is to be expected from the ubiquity of the pathologic lesions. Early in the disease the reflexes are increased, but quite characteristic is the ease with which their fatiguability occurs on repeated stimulation for their production. Pathologic reflexes indicative of pyramidal tract irritation (Babinski, Chaddock, Gordon, Oppenheim, etc.) are absent. Cranial nerve paralyses are nearly always met with, being among the most common manifestations of encephalitis. The oculomotor nerve is the one most often attacked. The abducens and facial nerve are occasionally disturbed.

A tremor is not infrequently seen. When it occurs, it is variable in character, distribution, and degree. In the cases I have seen, it is more likely to be a fine tremor, absent when the patient is at rest, but brought out magnificently when the sufferer attempts the use of his hands or forearms. Several authors have reported lemniscus symptoms developing, as shown by bilateral impairment of deep sensation. In Cadwalader's 3 cases there was inability to fully appreciate position, passive movement, and vibration. Ornstein has reported a case of a typical cerebellar character, with ataxia as the outstanding phenomenon. In this instance the Parkinsonian facies and tremor were absent.

The ocular disturbances merit further consideration. Oculomotor irritation or paresis produce a myriad of symptoms. Difficulty of accommodation, diplopia, and strabismus are striking in the acute attack, and may remain in the chronic phase, or be lit up anew in an exacerbation. Later on, we find spasms of the muscles. The spasms may be tonic or clonic, and in some cases they consist of short, rhythmic, tonic spasms.

The spasms cease during sleep, and are shortened by atropin and epinephrin. Optic atrophy may and does occur. As early as 1919 Smith, of Philadelphia, had presented such a case. Holden believes that optic neuritis and papilledema were caused by increased intracranial pressure. Others hold it to be due to the associated meningitic process.

A not uncommon finding, one which is very troublesome to the patient and resistant to therapeutic measures, is that of profuse salivation. Often we see these patients with their lower lip drooping, mopping the drooling secretions continuously. The sialorrhea has been explained by assuming an increased production of salivary secretions from nerve stimulation, but the biggest factor is probably the loss of the swallowing reflex, one of the normal means of eliminating excessive saliva.

We do not receive any assistance from the laboratory in diagnosticating Parkinsonian states. Cruchet and other early observers found a hyperglycorrhachia, but later studies showed the fasting level of glucose in the blood and spinal fluid to be within normal limits. I have found this to be so in the few cases in which glucose determinations were made. Those who persist in the belief of a high spinal-fluid sugar are of the opinion that a normal finding is indicative of a quiescent or dormant period in the disease process. The complement-fixation test is uniformly negative in these cases, and offers us a valuable point in differential diagnosis. In only one of 19 cases was the Wassermann positive. This patient, who was in his forties, probably combined encephalitic Parkinsonism and cerebrospinal syphilis.

The problems in differential diagnosis are many, but on close analysis the many disease pictures which the syndrome mimics can be ruled out. Such diagnoses as lateral and multiple sclerosis have been confused. The presence of constant head pains suggested a cerebral tumor in one case, and cerebrospinal lues was thought of in another. The absence of laboratory findings, and of signs of pyramidal-tract disintegration with a history suggesting an acute encephalitis in the background, are sufficient to rule out other conditions. The two outstanding

conditions for comparison, and those about which most has been written, are true Parkinson's disease (paralysis agitans) and psychotic pictures, especially schizophrenic catatonia (catatonic dementia præcox of the old terminology).

The similarity between paralysis agitans and Parkinsonian states is so great that some observers have considered the two identical, both as clinical and pathologic entities. Netter believes that, in certain instances, true Parkinson's disease is caused by the virus of encephalitis lethargica. Souques is more emphatic. To him, both the classic and postencephalitic types are clinical manifestations of one disease—paralysis agitans, the difference being in the degree of the lesion. He asserts that, when the encephalitic process in the mesencephalon is slight and "reparable," a Parkinsonian syndrome is produced; if the lesion is irreparable, paralysis agitans results. As stated above, the majority of writers consider the two conditions different, morbid entities, basing their views mainly on pathologic grounds. The lesions in paralysis agitans in later life depend on vascular degeneration of the pallidal mechanism; the lesion in encephalitis is most marked in the substantia nigra.

Clinically, however, the outstanding differences in the two conditions would lead us to believe they are distinct entities. The following table, modified from Gordon's excellent summary, will serve to distinguish between the two:

Encephalitic Parkinsonism.	*Paralysis Agitans.*
1. Age: Usually in second and third decades.	1. Age: Forty and beyond.
2. History: Develops months or years after an acute, febrile disorder.	2. History: Onset without precedent acute attack; extreme insidiousness.
3. Hypertonia: Predominates over tremor.	3. Hypertonia: Predominated by tremor.
4. Facies: Orbits not widely open, not frightened, appear in distress; mask-like.	4. Facies: Appear in wild fright, surprise, and anxiety.
5. Tremor: Slight, fine, rapid, or fugacious; horizontal or vertical; usually intentional.	5. Tremor: Coarse, not rapid, constant, pill-rolling in character; disappears in voluntary action.
6. Anteropulsion: Movement absent.	6. Anteropulsion: Movement present.
7. Drooling: Comparatively early.	7. Drooling: Late.

The psychotic pictures are not definite, and it would be amiss to attempt to place the various mental disturbances in definite, established psychotic groups. One is led to believe two things: First, that psychic upsets occur in those who are favorably disposed to such accidents by hereditary burdening; second, encephalitis probably activates organic disease of the nervous system, thus producing the attendant mental catastrophe. Our sheet anchor in determining whether a condition is encephalitic in origin is, of course, a knowledge of an encephalitic attack in the past, a thing which is likely to be overlooked by the practitioner. We have innumerable examples of conduct disturbances, especially in children and young adults, for which encephalitis is to be indicted. Similarly, arrested mental development and epileptic-like attacks demand study for a like origin. Ravine has reported a sudden outbreak of behavior problems in school children for which Parkinsonism was the cause. Therefore, as Goodhart and Cottrell have pointed out, the problem is not only of a medical nature, but also one of social and economic importance.

Nothing dogmatic can be asserted about the prognosis in these cases without fear of contradiction. The majority of cases recover from the acute attack, but nearly all show residual stigmata. Robb has given us the first statistics of cases he has observed for two and a half years. I think they are worth quoting in full:

Died in acute attacks	21
Of 152 who recovered:	
(*a*) Untraced	11
(*b*) Examined after two and one-half years	141
Of 141 examined:	Per cent.
(*a*) Apparently well	8.8
(*b*) Died of effects	4.9
(*c*) Suffering from mild nervous symptoms	7
(*d*) Showing changed character	12.7
(*e*) Showing mental symptoms	13.4
(*f*) In other medical institutions	13.4
(*g*) Subject to epileptic convulsions?	1.4
(*h*) Showing Parkinsonism	58
Stage I	21

Stage II	42	
Stage III	20	Per cent.
(*i*) Partially incapacitated for work or school		20.5
(*j*) Totally incapacitated for work or school		59.5

Robb expressed the belief that, if these cases were examined again at the end of five or ten years, the percentage would be further reduced. Other observers do not agree with his contention, because of the chronicity of the disease. There is no assurance that his cases, which were apparently well after two and a half years, would not develop symptoms of one sort or another. At any rate, his statistics bear out the seriousness of the disease from its social and economic aspects.

The mode of death is of two types. In the one, the patient slowly and steadily grows worse for a short period; the end then comes suddenly, and the terminal illness is measured by days. An abrupt rise of temperature, probably from secondary terminal infection, ends the patient's life in a few days. The other type of death is a vascular death. There is always great damage to the blood-vessels in Parkinsonism, and, consequently, vascular reactions may and do occur, even at an early age. They die of hemorrhage, but they are small, multiple hemorrhages, and not hemorrhage from rupture of a single vessel.

Very little can be done in the treatment of epidemic encephalitis and of its many residuals. Chemotherapy has been tried, but with very little success. Von Economo reported benefits from injections of large doses of urotropin in some cases, and of Pregl's solution of iodin in others. Mercurochrome has been tried with indifferent success. A favorite treatment in certain clinics is the use of massive doses of salicylates for the acute attack. Van Bogaert claims that no cases of encephalitis, in which salicylates and urotropin are combined in large doses, fail to yield results. Rosenow has produced a serum from his streptococcus. This has been used in acute cases with few favorable reports. Whatever favorable reports have come in, may be from cases showing remissions. As to the treatment of the Parkinsonian syndromes we resort to hyoscin in particular. This is a very valuable, palliative remedy, and tends to lessen

the rigidity and improve the mental attitude. Moll has reported on the use of nicotin in doses of 1/30 grain, ascending to 1/5 grain. He finds that it offers no permanent cures, but the immediate results, so far as rigidity is concerned, are good. For the troublesome drooling, atropin may be used. If this is not successful, carefully guarded doses of *x*-ray, just sufficient to lessen the secretion of the parotid gland, are applied in that region. One must not overlook the inestimable value of physiotherapy by massage and hydrotherapeutics combined with mental and physical rest, all of which are of greater benefit than any drugs.

Summary.—1. Epidemic encephalitis, a comparatively new disease, has become very rife, especially in this section.

2. The disease is characterized by marked chronicity, producing a multitude of interesting sequelæ.

3. Four clinical pictures are outstanding in the so-called postencephalitic syndrome:

(*a*) Generalized Parkinsonism without tremor.

(*b*) Generalized Parkinsonism with tremor.

(*c*) A localized type.

(*d*) A transitory type.

4. Encephalitic bradykinesia is differentiated by a difference in the location of the essential pathology (substantia nigra in the former, and globus pallidus in the latter). Clinically, the two can easily be differentiated.

5. The disease presents interesting and often confusing psychiatric problems.

6. The prognosis as to life expectancy is fair; as to recovery from the sequelæ, poor.

Conclusion.—It is important to recognize the encephalitis in its acute stage, with a view of clarification of its identity, and to furnish us with a basis for many conditions which arise long afterward.

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DIVERTICULOSIS OF THE LARGE BOWEL

THIS paper deals with an important, uncommon, but not rare abnormality of the large intestine, commonly referred to as diverticulosis.

Historic.—Virchow, in 1853, noted in cases at autopsy an "isolated, circumscribed, adhesive peritonitis" affecting the colon. Graser, in 1899, demonstrated the association of the condition noted by Virchow, with acquired multiple diverticula of the colon. Sir Berkeley Moynihan, in a paper entitled "The Mimicry of Malignant Disease of the Large Intestine," read before the Clinical Society of London in 1907, gave impetus to the dissemination among the profession of knowledge concerning the condition. In America, Beer, Fischer, and W. J. Mayo were the outstanding early students of the condition, and in France, Patel. Since 1910, a great deal of pertinent information has been published in a succession of papers from the Mayo Clinic, instigated by W. J. Mayo. Outstanding in the literature is an article (British Journal of Surgery, 1917) by Telling and Gruner, two British observers. Even now the existence of the condition as a distinct clinical entity is not universally recognized among the profession at large, and only since about 1917 has it been very generally described in text-books of medicine and surgery. It interests both surgeons and internists.

Pathology and Etiology.—Correllated observations of different workers have emphatized the following pertinent facts:

1. In some individuals there exists an hereditary, constitutional weakness in the smooth-muscular portion of the wall of the hollow viscera. This fact is evidenced, by frequent observa-

tion, that in the same individual there may exist hundreds of acquired diverticula of the entire bowel, and also diverticula of the urinary bladder and esophagus.

2. In the normal colon,[5] there exist naturally weak places in the muscular wall which predispose, in the presence of contributory factors, to herniation of the bowel contents and mucosa through the muscularis—just as the inguinal canal in the abdominal wall predisposes to the formation of inguinal hernia. It will be remembered that the smooth muscle of the colon is arranged in two principal layers—an inner, continuous, circular layer and an outer, longitudinal layer which is aggregated into three longitudinal bands, one of which lies at the mesenteric attachment—the other two about equidistant from the mesenteric band and from each other. Blood-vessels enter the bowel wall at the mesenteric attachment, some penetrating the mesenteric longitudinal band to enter the submucosa, and the tunnels made by the vessels are here amply reinforced by the mesenteric band. Others course subperitoneally and the larger of them penetrate the muscularis to enter the submucosa, just before they reach the lateral, longitudinal band on either side. The paths made by these vessels have no reinforcement and constitute the naturally weak places in the bowel wall, explaining, in the presence of other contributory factors, the occurrence of multiple, flask-shaped pouches of mucosa herniated through the muscularis, lying subperitoneally, almost always between the mesenteric and the lateral band on either side of the bowel. The pouches are often concealed by the subserous fat and appendices epiploicæ—which also lie chiefly between the mesenteric and lateral longitudinal band on either side.

3. The contributory factors referred to above are:

(*a*) *Constipation*,[8] with distention of the bowel and gas formation, giving rise to increased intracolic pressure. The accumulation of feces in constipation is greatest in the sigmoid colon and rectum—which fact, together with the fact that the colon is effectively segmented by the haustræ into compartments, explains the limitation of the diverticula in about 90 per cent. of the cases[8] to the large bowel below the splenic

flexure, and chiefly to the sigmoid, making the clinical picture of diverticulosis of the large bowel predominantly that of a left-sided, abdominal involvement, usually iliac.

(*b*) *General obesity*,[10] with an accompanying increased amount of fat in the bowel wall, is a factor. The average weight in a large series from the Mayo Clinic[8] was about 170 pounds.

(*c*) *Age*[8] is a factor in the development of the clinical picture, indicating that the above factors, in most cases, are operative over a long period of time before a full clinical picture is developed. The average age of 289 cases at the Mayo Clinic was fifty-two years.

Summarizing, then, in diverticulosis, the colon below the splenic flexure shows multiple, acquired, flask-shaped, rice-grain to hazelnut-sized pouches of mucosa projecting through the muscularis, lying subperitoneally—some of them concealed by appendices epiploicæ or fat in the wall of the bowel. Their development is favored by hereditary weakness of the smooth muscle of the body, by obesity and by constipation, and requires a considerable period of time during which the above factors are operative. Exceptions occur to all of the above statements, and youth, lack of obesity, and lack of constipation do not preclude the existence of the condition.

Clinical Course with Cases.—It must, first of all, be emphasized that not all individuals with multiple diverticula of the large intestine present symptoms—although they are certainly liable to the development of distinct clinical symptoms at some later period. The roentgenogram shown here (Fig. 211) is from a white female, aged fifty-two years, weight 195 pounds, who came to the hospital because of symptoms of gall-bladder disease. Barium enema revealed, as shown, multiple diverticula of the large intestine, an accidental finding in the course of a routine examination. She had a diseased gall-bladder, which was removed with complete relief from symptoms. The diverticula in this case probably produced no symptoms.

It must be clearly understood that the development of symptoms is entirely dependent on *complications* of the simple picture described, and the chief of these complications is infec-

tion, with inflammation, which may be acute suppurative, subacute, or chronic. The extent of the inflammation and the involvement of adjacent structures give rise to the different clinical pictures produced by the process. It must be recognized that anything can happen to one or more of these diverticula that can happen to the vermiform appendix. The saccular

Fig. 211.

pouches are practically devoid of muscular coat, and, thus, have no self-emptying mechanism, and are prone to become impacted with foreign bodies[13] as grape-seeds, etc., or with inspissated feces. The ostium of communication with the bowel is usually small, favoring stasis within the diverticulum. Stasis favors multiplication of virulent organisms[13] with resultant infection and inflammation. W. J. Mayo has described four clinical

pictures occurring in the course of diverticulosis of the large bowel, to which other observers[13] have added others, and which, taken together, summarize the hazards to which an individual bearing the symptomless diverticula is subject as a result of their presence. They are:

1. **Acute Inflammation (Acute Diverticulitis and Peridiverticulitis).**—Just as in the case of the appendix, acute inflammation may occur in one or more of the diverticula. Its occurrence is associated with a peritonitis—easily understood when the subperitoneal situation of the diverticula is remembered—and pain. There is, as a rule, an acutely sensitive tumor which subsides with subsidence of the acute stage. The acute attacks are very prone to recur, but the danger of perforation with generalized peritonitis is rather remote—for adhesions quickly form. The local symptoms are usually referred to the left iliac fossa, as in the following case of Bland-Sutton: Male, forty. Acute pain, swelling, and tenderness in the left iliac region, suggesting *appendicitis with transposed viscera.* At the operation there was an acutely inflamed diverticulum on the descending colon, which extended into an epiploic appendage and contained feces and a foreign body. Resection of the appendage with the diverticulum was followed by recovery. Numerous such cases exist in the literature. The repeated acute attacks are steps in the development of the clinical pictures yet to be described.

2. **Diverticulitis and Peridiverticulitis with Abscesses (Resulting in Enterovesical, Entero-enteric, and Other Fistulas).**—It may readily be seen how the mobile loop of sigmoid with its patches of sticky exudate, in acute attacks, may adhere to the upper surface of the bladder or to other loops of bowel or to the abdominal wall. Due to the presence of feces and virulent organisms within the diverticula underlying the areas of peritonitis, the inflammation persists, and may result in abscesses which dissolve the walls of the adhered structures and place their lumina in communication. Numerous cases exist in the literature illustrating this phase of the pathology of diverticulitis —and providing difficult cases for operative treatment.

The next two groups, described by W. J. Mayo, are discussed together, due to their close resemblance.

3. **Obstruction due to diverticulitis,** and

4. **Carcinoma on Diverticulitis.**—These two groups constitute the most important phase of the pathology of diverticulitis, due to the fact that the former has as frequently been misdiagnosed as the latter.

It is readily seen how—once the inflammatory process is initiated within the diverticular and peridiverticular structures, and in the presence of fecal stasis and imperfect drainage within the diverticula—the process is perpetuated in chronic form, with acute exacerbations superimposed. In course of time the fat of the bowel wall, the bowel wall itself, and the loose retroperitoneal tissue become infiltrated with wandering cells. There is a hyperplasia of the fibroblasts, and increased production of new blood-vessels, and there results a permanent mass which may produce obstruction of the bowel, and so nearly simulate malignancy as to render differential diagnosis impossible. Quoting McGrath,[12] "Cases have been diagnosed malignant clinically, surgically, and at autopsy, and later pathologic examinations have proved the process to be simple inflammation."

The above exactly describes the case of a prominent New Orleans surgeon who was explored for an obstructing mass in the left iliac region, a gross, surgical diagnosis of malignancy made, and colostomy performed, to prolong life and make his last days more comfortable. With the fecal current diverted away from the mass, improvement occurred. The patient went then to other hands for treatment, a second exploration was done, the mass found removable, entero-anastomosis performed between the cut ends of the sigmoid, and the colostomy closed. Pathologic examination showed no malignancy. Recovery of health was complete.

Another case in point is that of a Louisiana physician, aged sixty-five, who for about five months had had a palpable mass in the left iliac region, associated with obstinate constipation. Two acute attacks of localized pain and tenderness over the mass occurred, after each of which the mass diminished in size.

He came to the hospital during an interval between attacks and barium enema showed obstruction with filling defect in the sigmoid colon, associated with numerous diverticula of the sigmoid. He is at present receiving medical treatment, with the hope that the mass will diminish in size and operation will be possible later. Roentgenogram (Fig. 212) was made in the study of his condition.

Fig. 212.

The presence of diverticula does not exclude the existence of cancer, which was present in 30 per cent.[10] of an early series of 42 cases at the Mayo Clinic, and in about 14.5 per cent. of a later series of 116 cases.[8]

W. J. Mayo states, "I do not know of a more difficult clinical differentiation than to foretell whether a given obstructing tumor,

deep in the iliac fossa of an adipose patient, is diverticulitis, or carcinoma, or both."

Regarding the causal relationship between diverticulitis and malignancy, McFarland[11] states that those best fitted to judge are deepest in their conviction that the chronic irritation is a potent factor in initiating the cancer process, and W. J. Mayo states his belief that such is the case.[10]

Other more remote manifestations of diverticulitis of the large bowel are those cases in which, without local symptoms, the diverticuli act as foci of infection which may be a pyemia, acute or chronic, with general poor health, anemia, and vague body-aches. Diagnosis and treatment will be discussed briefly, touching only upon salient features.

Diagnosis.—The following points should be kept in mind:

(*a*) *Age.*—Below thirty-five years the diagnosis is doubtful. Most clinical cases occur between forty and sixty-five.

(*b*) *Sex.*—About 65 per cent. are males.

(*c*) *Nutrition.*—The majority are well nourished.

(*d*) *Constipation* is obstinate in over 50 per cent., but may alternate with diarrhea.

(*e*) *Attacks of colicky, left-sided, abdominal pains* are very suggestive, especially if recurrent over a long period of time.

(*f*) The condition should be kept in mind as a possible explanation for any *left-sided, abdominal tumor*, especially if it shows acute swelling and pain occurring in attacks with recession of symptoms between attacks.

(*g*) Radiographic study[3] with opaque enema reveals diverticula in the majority of cases.

Differential Diagnosis.—(*a*) *Carcinoma of colon* shows a fairly short period between commencing symptoms and severe complications, anemia, blood and pus in stools, and obstruction. Carcinoma is ulcerative, while the pathology of diverticulitis is largely extramucosal, without blood or pus in stool.

(*b*) *Actinomycosis* usually attacks cecum. Any age is involved. There may be ray-fungi in the stools.

(*c*) *Syphilis* by the presence of other stigmata, the Wassermann reaction, and therapeutic test.

(*d*) *Tuberculosis*, by inoculation of a guinea-pig with feces, and by tuberculin skin-test.

(*e*) *Left-sided appendicitis* usually occurs, with complete visceral transposition. Exploration may be required.

(*f*) *Tumors and inflammation of the adnexa in the female* by gynecologic examination and history.

Treatment.—The fundamental principle of treatment is that all diverticula, giving symptoms, should be removed. Removal may be a very difficult surgical feat—or may be impossible in acute obstruction which demands temporary colostomy, or ileostomy. At the Mayo Clinic diverticulectomy is preceded by a preliminary ileostomy or colostomy. Their records show a mortality of 10 per cent. following this procedure. In the acute attack the Ochsner treatment for acute appendicitis after the first twenty-four hours of the attack is advised.[8]

Symptomless diverticula require no treatment. While awaiting operation following an acute attack, medical treatment is in order. It consists of free saline purgatives, attention to general hygiene, and an anticonstipation diet.

Summary.—1. Diverticulosis of the colon with complications is not a rare condition, and is a definite clinical entity.

2. It may manifest itself in varying ways, and is especially liable to mimic malignancy.

3. Operation in expert hands offers a 90 per cent. cure.

4. It must be kept in mind in the diagnosis of any left-sided intra-abdominal tumor or inflammatory process.

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